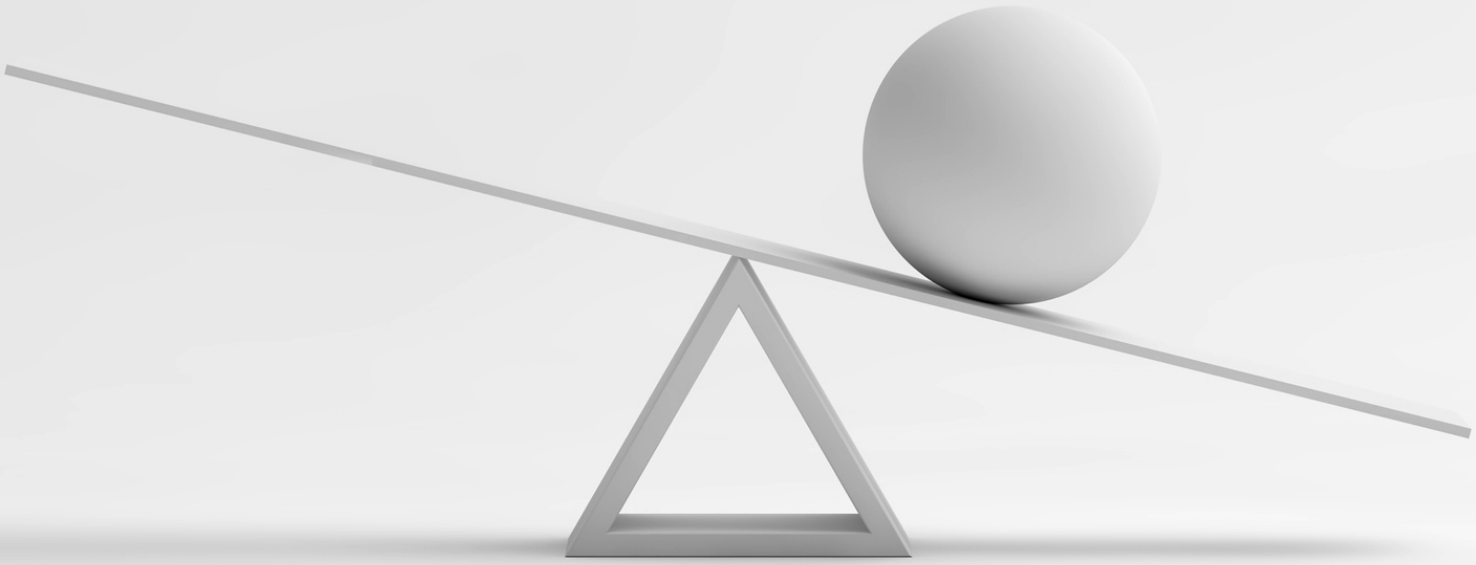
JULY/AUGUST 2022 VOL. 8, NO. 4

VALUE & OUTCOMES SPOTLIGHT

A magazine for the global HEOR community.

Efficiency Versus Health Equity in HTA



ISPOR

Improving healthcare decisions

VALUE & OUTCOMES
SPOTLIGHT

JULY/AUGUST 2022
VOL. 8, NO. 4

TABLE OF CONTENTS

EDITOR-IN-CHIEF
Zeba M. Khan, RPh, PhD

EDITORIAL ADVISORY BOARD
Soraya Azmi, MBBS, MPH (United States)
Ágnes Benedict, MSc, MA (United Kingdom)
Koen Degeling, PhD, MSc (Australia)
Aakash Bipin Gandhi, BPharm (United States)
Ramiro E. Gilardino, MD, MSc (Switzerland)
Karin Groothuis-Oudshoorn, PhD (The Netherlands)
Eric Jutkowitz, PhD (United States)
Yvonne YL Lee, PhD, MPH (Singapore)
Sandra Nestler-Parr, PhD, MPhil, MSc (United Kingdom)
Lucinda Orsini, DPM, MPH (United States)
Louise Parmenter, PhD, MSc (United Kingdom)
Marisa Santos, MD, PhD (Brazil)
Stephen W. Schondelmeyer, PhD (United States)
Soham Shukla, DPharm, Msc (United States)

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

EDITORIAL STAFF

Lyn Beamesderfer
Director, Publications
lbeamesderfer@ispor.org

Detra Davis
Senior Manager, Publications
ddavis@ispor.org

ISPOR CORPORATE OFFICERS

Nancy S. Berg
Chief Executive Officer/
Executive Director

Sue Capon
Chief Operations Officer

Richard J. Willke, PhD
Chief Science Officer

Laura T. Pizzi, PharmD, MPH
Associate Chief Science Officer

Betsy Lane
Director and Chief Marketing
& Communications Officer

ISPOR HEADQUARTERS

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

VALUE & OUTCOMES SPOTLIGHT
PUBLISHING, SUBSCRIPTION, AND ADVERTISING OFFICE:
Value & Outcomes Spotlight
Online: ISSN 2375-8678
Published bi-monthly by:
ISPOR
505 Lawrence Square Blvd, S
Lawrenceville, NJ 08648 USA

Direct photocopy permission and reprint requests to Director, Publications.

Cover photo courtesy of iStockphoto/ChubarovY
Signal illustration courtesy of iStockphoto/DrAfter123

© 2022 International Society for Pharmacoeconomics and Outcomes Research.

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

FROM THE EDITOR

Improving Health Equity

Health equity—providing equitable and accessible high-quality healthcare—is a business and moral/ethical imperative. Each stakeholder in the healthcare system should do their part to advance health equity in their organizations, businesses, communities, and society. Some argue that little has changed in health equity over the past 20 years since the Institute of Medicine published its report, *Unequal Treatment*, highlighting that racial and ethnic disparities exist in healthcare. For example, Blacks and Hispanics generally receive poor quality of care when compared to Whites across many diseases. Although many are striving to improve the narrative and make positive changes, undeniably, health disparities still exist today. Literature has clearly documented these inequities by providing data and definitive statistical analyses showing that minorities such as Blacks, when compared to non-Hispanic Whites, have lower life expectancy, higher cancer mortality rates, increased infant mortality, and greater likelihood of having diseases. Distrust in the healthcare system among minority groups further adds to health disparities and was evidenced during the COVID pandemic by the hesitancy of these groups toward being vaccinated. What can we as health economists and health researchers do to make a difference and reduce the disparities and provide more equitable access to healthcare?

Ensuring inclusion of diverse populations in clinical trials is one area where an immediate and substantial improvement can be made. Diversity in clinical trials has also been promoted by government agencies such as the European Medicines Agency and the US Food and Drug Administration, which have both published guidance related to diversity, equity, and inclusiveness in clinical trials. Heeding diverse patient voices and perspectives throughout the entire drug development process is much more valuable and effective than obtaining ad hoc patient feedback after the drug launch. Adherence to this practice will most certainly generate meaningful data to assess and increase the applicability and appropriateness of treatments and therapeutics for minority patients.

Improving our methodologies for health technology assessment (HTA) by incorporating equitable healthcare resource distribution in HTAs is also key in ensuring health equity. The inequalities that may exist during these assessments need to be quantified and addressed. Using various methods that can range from a simple distribution analysis in modeling to using multicriteria decision analysis and weighting willingness-to-pay thresholds to reflect health equity considerations and disease burden can help ameliorate health equity. We can drive the application of methods that directly address health equity by ensuring that inclusive perspectives are integrated into HTAs and become part of the evaluation process.

To make a positive change, our approach to healthcare equity will require not only a strong commitment, but also active engagement, participation, accountability, and a call to action among all stakeholders in the healthcare ecosystem. Through our dedicated and persistent vigilance, greater health equity will undoubtedly lead to improved patient outcomes and healthier communities.

As always, I welcome input from our readers.
Please feel free to email me at zeba.m.khan@hotmail.com.

Zeba M. Khan, RPh, PhD
Editor-in-Chief, *Value & Outcomes Spotlight*

ISPOR SPEAKS

HEOR + ISPOR = Making an Impact

Jan Elias Hansen, PhD, Vice President, Genentech, South San Francisco, CA and President (2022-2023), ISPOR, Lawrenceville, NJ, USA

I am so honored and excited to begin my term as your ISPOR President for the 2022-2023 term. It was wonderful to connect with so many of you at ISPOR 2022, the Society's first "hybrid" conference, where participants attended sessions in person and virtually.

Vision

I am passionate about making an impact and believe that the discipline of HEOR and ISPOR as a global organization are well positioned to do this now. ISPOR and our community of highly trained and skilled HEOR professionals can impact today's healthcare landscape in both big and small ways by informing the wide range of issues healthcare decision makers are increasingly confronted with in our challenging world, especially on the heels of the COVID-19 pandemic.

In my presidential vision statement, I outlined how we can accelerate the impact of HEOR by:

- ***Engaging*** healthcare stakeholders
- ***Applying*** HEOR to address challenges and pain points
- ***Informing*** healthcare issues through the use of HEOR data and approaches that are scientifically rigorous and sound

ISPOR Resources

My vision statement certainly reflects an audacious challenge. While we may take for granted the impact we already make both from an individual perspective and on each other as a community of HEOR professionals, we are making an impact on a broader level where bold improvements are already happening—thanks to better informed healthcare decision makers who are benefiting from the efforts and robust research produced by ISPOR members.

In accordance with ISPOR's Strategic Pillars, there are numerous ISPOR resources and tools that are helping our colleagues from around the world invest in their own skills and find enriching careers that allow them to put the HEOR discipline at the forefront of enabling informed healthcare decisions. Some of these examples include:

- The "Top 10 HEOR Trends" report is being shared with healthcare stakeholders and industry executives as a way of educating diverse audiences about HEOR topics

- The competency framework has been used as the basis for surveying HEOR fellows, influencing the structure and curriculum of fellowships, and ultimately helping individuals secure jobs in this field

- ISPOR Short Courses are being leveraged to expand knowledge and build expertise in the understanding and use of specific HEOR topics, methods, and approaches, ultimately expanding capabilities and skills and supporting ISPOR members in their technical growth and development

- And finally, ISPOR Special Interest Groups are providing communities for HEOR professionals to "dig in" and connect with others where they have great passion or where they want to learn more, ultimately extracting value for themselves and for the stakeholders who benefit from all that HEOR insights have to offer

The real power of this profession is revealed when it can be leveraged in bigger, bolder ways to transform and make "real" change to healthcare systems and healthcare decisions around the world.

Impact

At ISPOR 2022, I presented a few powerful examples of how HEOR—facilitated directly through ISPOR membership—is having an impact.

- Eric Jutkowitz with Brown University and Laura Pizzi (now at ISPOR) worked with a team of researchers at the University of Connecticut to conduct a comprehensive cost analysis on the Caring for Older Persons in their Environment (COPE) program.[1] The results of this work were used to make the case to successfully obtain federal funds supporting state-wide implementation of the program through the existing care management infrastructure, impacting and improving the access patients requiring dementia care have to this program in Connecticut

- Jaime Caro and his team, at the request of a National Health Service (NHS) Foundation Trust, developed a model that assisted in the planning and estimated needed hospital resources (eg, critical care beds) for managing patients with COVID-19.[2] A simulation model plotted actual patient trajectories and resulted in capacity estimates for critical care beds. NHS hospitals were able to expand bed capacity to better prepare for waves of COVID-19

- ISPOR regional chapters have recently been involved in the development of national guidelines in an expansive set of countries including Algeria, Chile, Czech Republic, Ghana, India,

Hungary, South Africa, New Zealand, and Thailand. Through the engagement of ISPOR chapters with these national governments, ISPOR members have been able to influence health technology assessment, pricing and reimbursement, and economic evaluation approaches used in these countries

How You Can Make an Impact

There are many possibilities for making an impact, and they are happening each and every day across the world. As I begin my Presidential term, my ask of you as an expert in the field of HEOR is to:

Develop yourselves as leaders in this profession

- Invest in your own expertise and skills
- Be ready to explain to other stakeholders across the healthcare continuum why this work makes a difference. This will further strengthen the value and credibility of the HEOR profession

Be passionate and curious about the impact your work can have

- Determine how your work should be shared and leveraged—and push for its use even beyond the traditional means of scientific publications

Advocate and evangelize for your work and this profession!

- Think about how what you do today can make a direct impact on a future healthcare question, issue, or decision
- Evangelize and share your experiences and the impact you are having with me, with the HEOR community, and with the world

My Commitment to You

I also make a commitment to you: **to frequently and consistently communicate with you on the impact that the HEOR discipline and ISPOR has in the world**. We are also asking you to share your "stories of impact" with us—some of which may be included in my communications as impactful case examples of how HEOR is making a change and improving healthcare decision making. If you have a story of impact that you would like to share, please email it to me at leadership@ispor.org.

I am sincerely enthused about hearing from you and sharing how you're making a difference. Together we can amplify the voice of HEOR and of ISPOR as we work to achieve our mission and goals to improve decision making for health globally.

Let's plan to meet in Boston in a year to celebrate your successes and the advancement of the HEOR discipline in informing some of the toughest healthcare issues of our time!

References

1. Pizzi LT, Jutkowitz E, Prioli KM, et al. Cost-benefit analysis of the COPE program for persons living with dementia: toward a payment model. *Innov Aging*. 2021;Oct 16;6(1):igab042. doi: 10.1093/geroni/igab042

2. Caro JJ, Möller J, Santhirapala V, et al. Predicting hospital resource use during COVID-19 surges: a simple but flexible discretely integrated condition event simulation of individual patient-hospital trajectories. *Value Health*. 2021;24(11):1570-1577.

What you need...
you know we got it:
Respect of the global HEOR community.

Leverage ISPOR's reputation and reach to maximize your visibility, impact, and connection within the HEOR field.

ISPOR
Improving healthcare decisions

HEOR NEWS

1 NICE's Early Value Assessment for Medtech: Panning for Nuggets of Innovation Gold (NICE)

Jeanette Kusel, Mark Salmon, and Sarah Byron at NICE write about how the organization's Early Value Assessment for Medtech will rapidly evaluate the value and clinical effectiveness of digital products, devices, and diagnostics.
Read more

2 Lack of Innovation Set to Undermine Antibiotic Performance and Health Gains (WHO)

The organization says in its annual pipeline report that the rate of development for new antibacterial treatments is not growing fast enough to address the threat of antibiotic resistance.
Read more

3 Industry-Funded Studies on Cost-Effectiveness Often Favor Pricier Drugs, Study Finds (Pharmalot)

A study in the *BMJ* found that one-third of the cost-effectiveness studies done by pharma companies ended in more favorable results than independently done analyses, with industry-sponsored studies twice as likely to report that a medicine was more cost-effective when using the quality-adjusted life year to determine a medication's value.
Read more

4 Dubai Health Authority Launches First-of-Its-Kind Value-Based Healthcare Model (Arabian Business News)

The EJADAH program will assist healthcare service providers to frame evidence-based guidelines for physicians to follow with regard to treatment protocols for all ailments, in an effort to enhance healthcare and reduce unnecessary costs.
Read more

5 Parliamentary Panel to Discuss Affordability of Cancer Treatment With Health Secretary (ET Healthworld.com)

India's Parliamentary Committee on Health and Family Welfare met to discuss the rising cost of cancer care in the country and the growing proportion of the cost of nonmedical services for this care.
Read more

6 Saudi Arabia to Invest $3.4 Billion Into Vaccines and Vital Medicines (Arabian Business News)

The goal of the investment is to achieve pharmaceutical and health security for the kingdom, with the first phase localizing the production of vaccines, plasma, and insulin technologies.
Read more

7 Potential Medicare Part D Savings on Generic Drugs From the Mark Cuban Cost Plus Drug Company (*Annals of Internal Medicine*)

According to this analysis, if Medicare had bought generic medications through the Mark Cuban pharmacy, it could have saved up to $3.6 billion in 2020.
Read more

8 European Researchers Seek Greater Stake in Drug Development in Bid to Improve Access (STAT News)

Universities in Europe want more control over their intellectual property that is being used in drug research in an effort to improve access to the final product. However, these institutions are not finding this quest easy.
Read more

9 Lawmakers "Disheartened" by CMS Oversight of Medicare Advantage Amid Coverage Denials, Overpayments (Fierce Healthcare)

Members of the US House of Representatives want the Centers for Medicare and Medicaid Services to increase its scrutiny of Medicare Advantage plans, sparked by reports of overspending and consumer complaints of coverage denials.
Read more

10 Commonwealth Leaders Recommit to Ending Malaria and Neglected Tropical Diseases (WHO)

Heads of state and government from Commonwealth countries have reaffirmed their commitment to ending malaria by 2030.
Read more

FROM THE JOURNALS

A Case of Multitasking: Conducting and Using HTA and HEOR in Pluralistic Healthcare Systems

Michael F. Drummond, MCom, DPhil, University of York, England, United Kingdom for the ISPOR HTA Council Working Group on HTA in Pluralistic Healthcare Systems*

Background

Much of the discussion of the use of health technology assessment (HTA) in pricing and reimbursement decisions for pharmaceuticals and other health technologies is in the context of healthcare systems with one major payer or HTA agency. We read about the analyses conducted for or by, and decisions made by, IQWiG/G-BA in Germany or NICE in England.[1,2] We also read about the similarities and differences of decisions made by the payers/agencies in different countries.[3,4] In these (largely) "single-payer" healthcare systems, the conduct and use of HTA is relatively straightforward. The manufacturer submits clinical data (plus an economic model in jurisdictions that require them) to the HTA agency or payer according to the required guidelines, and merely waits for the outcome.

However, if one takes a broad, worldwide view, healthcare systems with one major payer or HTA agency are in the minority. Most healthcare systems are "pluralistic," with many payers. The most well-known example is the United States, which has a multipayer private healthcare system operating alongside a public system, plus systems serving particular categories of individuals, such as military veterans. The conduct and use of HTA/HEOR in pluralistic healthcare systems is likely to be more complex, since the different payers may have different needs, data requirements and objectives. They may also have budgets of different sizes, with implied differences in willingness to pay for new health technologies. In addition, in pluralistic systems, the resources for conducting HTAs/HEOR are more thinly spread, raising doubts about whether a rigorous assessment can be performed in all cases.

This topic was selected for further study by the ISPOR HTA Council, which established a Working Group to consider these issues and to make recommendations for how the conduct and use of HTA could be improved in pluralistic healthcare systems. The group has recently produced its report and the main findings are summarized here. For more details and an extensive list of references, please consult the full paper.[5]

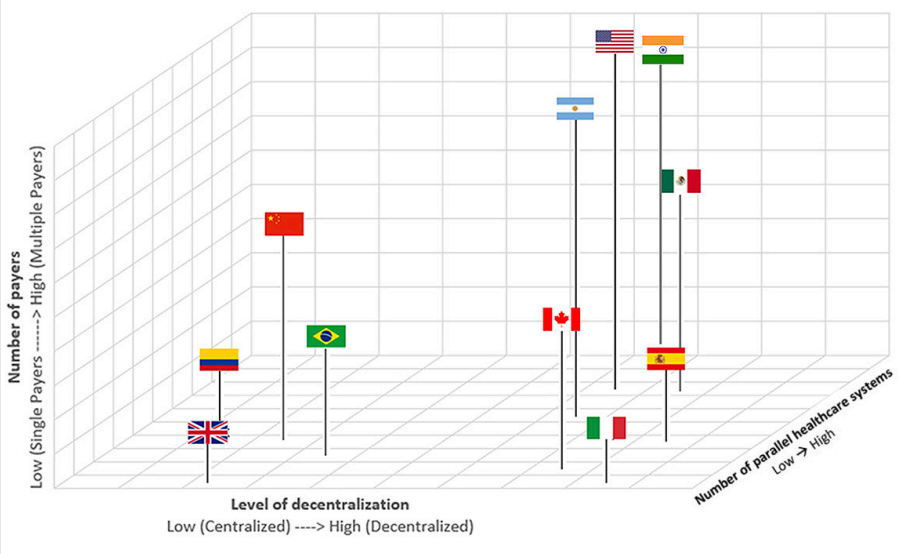
Working Group on HTA in Pluralistic Healthcare Systems

The Working Group began by characterizing the types of pluralism observed in healthcare systems worldwide. Private multipayer systems have been mentioned already. These exist most prominently in the United States, but also in some Asian countries. The second type of pluralism, called "parallel healthcare systems," is most common in Latin American healthcare systems. Here, there is often a public sector for serving disadvantaged populations and for implementing public health interventions, but the major healthcare system is often based on social security financing, based on workers' and employers' contributions. Most Latin American countries also have an extensive private healthcare system and some have health services for key groups of workers (eg, government employees, the military). The various mixes of these types of funding vary a lot from country to country. For example, the public sectors in Brazil and Colombia are quite extensive and these countries might be considered close to being "single-payer" systems.

The third type of pluralism is seen in "decentralized healthcare systems," where the responsibility for the financing and provision of healthcare is devolved by the central or federal government to states, provinces, regions, or territories. Good examples of this approach exist in Canada, India, Italy, and Spain. Although most of the funding is allocated centrally, the main decision-making power concerning the adoption of new health technologies rests with the regions, states, or provinces that frequently have their own HTA bodies.

One of the key insights from this exercise was that several countries exhibited more than one type of pluralism, and that levels of pluralism vary from country to country. Therefore, although it was possible to categorize countries by their main type of pluralism, the real distinctions between countries were much more nuanced. Therefore, the Working Group developed a 3-dimensional taxonomy that could be displayed in a diagram. The **figure** below, from the main report, categorizes countries in the 3-D pluralism space, according to: (1) the number of payers;

Figure. Different types of pluralism across selected countries



(2) the number of parallel healthcare systems and (3) the level of decentralization. The actual judgments the group made about particular countries, which are outlined in detail in the report, could be debated, but the figure nicely illustrates how the nature and level of pluralism varies by country—with those countries with low pluralism being closest to the origin of the figure, those with highest level of pluralism being furthest away. (This 'honor' goes to the United States). The other interesting insight from the figure is that the United Kingdom, which we normally think of as a "single-payer" country, does exhibit some pluralism, in that many responsibilities for healthcare are devolved to the 4 nations of the United Kingdom and it also has a small private sector.

Prior to formulating its recommendations, the group searched for examples of where particular countries had made attempts to deal with the main challenges of conducting and using HTA/HEOR in pluralistic healthcare systems. These examples are too numerous to discuss here, but we mention 2 particularly notable examples. First, there are the activities of the Canadian Agency for Drugs and Technologies in Health (CADTH), which over the years has developed guidelines for the economic evaluation of pharmaceuticals, conducted some demonstration projects in HTA/HEOR and, most importantly, coordinated drug review programs with the participation of provinces and territories. However, CADTH does not have decision-making responsibility, which remains with the provinces and territories. Second, in the United States, in the absence of many federally led efforts in HTA/HEOR, the Academy of Managed Care Pharmacy has developed a format (ie, guideline) for formulary submissions to private health plans and an independently funded body, the Institute for Clinical and Economic Review, has conducted HTAs/HEORs of several new technologies for use by private health plans.[6]

Recommendations

The group made several recommendations, organized under 5 main themes (**See Box**).

In making its recommendations, the Working Group acknowledged this was just the start in our understanding of the complexities in the conduct and use of HTA in pluralistic healthcare systems. However, it hoped that relevant jurisdictions may consider the recommendations for adoption, in their own way and in their own time. After all, that's the nature of pluralism!

1 Establishing a national focus for HTA

In single-payer systems, this is achieved by the national government or social insurer establishing an HTA agency. The remits of these bodies vary, but they all provide a focus for HTA efforts in the jurisdiction concerned. The group recognized that in countries with pluralistic healthcare systems there was often a reluctance of the government to get involved in HTA. In some countries, that involvement may not even be welcome! Therefore, the group was agnostic about how a national focus should be established (eg, it could be led by a respected professional society) but felt that such a focus was necessary to promote and to coordinate HTA efforts in all jurisdictions, especially those with pluralistic healthcare systems.

2 Developing a uniform set of HTA methods guidelines

While the nature of pluralism is that different decision makers may have different needs and requirements, in reality the scope for argument about appropriate methods is quite limited. Also, the benefits of giving all those conducting HTAs/HEOR in a given setting clear guidelines far outweigh the benefits of allowing more flexibility in approach. Some methods issues over which there are genuine differences of opinion, such as the inclusion or exclusion of productivity costs and benefits, could be handled in sensitivity analyses.

3 Ensuring that the HTAs are produced in a timely fashion

In single-payer systems, producing timely HTAs is rarely a problem because until the main payer decides to include the new technology for reimbursement, its use will be limited. However, in pluralistic healthcare systems, payers will be making adoption decisions when it suits their needs. Therefore, a new technology may be widely used before the HTA report is available. Historically, this has posed a problem in the United States' private sector, where some early adopters approve new technologies very quickly, based on their own business considerations, rather than waiting for HTA reports.

This is proving to be one of the major issues in pluralistic systems and the only solutions the group proposed were to (1) start the HTA early (perhaps before licensing approval for the new technology has been given); (2) produce a preliminary assessment, albeit based on limited data, in time to help the early adopters; and (3) revise the HTA as more evidence becomes available.[6]

4 Facilitating the use of HTA in the local setting

Given that the resources in pluralistic healthcare systems are likely to be thinly spread, it is very unlikely that many payers will have the resources to conduct their own local HTA. Therefore, every possible effort needs to be made to assist the local adaptation and use of HTAs conducted elsewhere. There are a number of possibilities here, such as making interactive models available, training local decision makers in the adaptation and interpretation of HTAs, and developing local cost and epidemiological databases to help populate models with local data.

5 Developing a framework for encouraging transparency in HTA

One of the advantages in single payer countries is that (depending on the country) any HTAs conducted—and the resulting decisions—are made public and shared with any decision makers having an interest. However, in pluralistic systems there are a number of potential barriers to transparency. In multipayer private systems, there may be a reluctance, for commercial reasons, to reveal the details of any analyses that support coverage decisions and the extent to which the decisions are influenced by such analyses. Also, in decentralized and parallel healthcare systems, it may be uncomfortable to reveal that certain new technologies are available in some settings and not others because of different levels of willingness to pay. Inequalities between rich and poor regions of countries, and between different population groups based on insurance coverage, may be inevitable in pluralistic healthcare systems, but are difficult to discuss publicly. The group recognized this but argued that (if possible) the results of HTAs should be made available on a secure website, anonymously if necessary, so at least payers can be aware of what other payers have done and the results obtained.

**Members of the ISPOR HTA Council Working Group on HTA in Pluralistic Healthcare Systems:* Michael Drummond, MCom, DPhil, University of York, United Kingdom; Federico Augustovski, MD, MSc, PhD, Institute for Clinical Effectiveness and Health Policy, Argentina; Devarshi Bhattacharyya, BDS, MPH, MSc, Kalam Institute of Health Technology, India; Jonathan Campbell, PhD, MS, Institute for Clinical and Economic Review, USA ;Nathorn Chaiyakanapruk, PharmD, PhD, University of Utah, USA; Yingyao Chen, PhD, Fudan University, China; Rosa Maria Galind Suarez, BSc, MHEM, Ministry of Health, Mexico; John Guerino, MHS, COEUS Consulting Group, USA; Aurelio Mejia, MSc, Ministry of Trade, Industry and Tourism, Colombia; Michelle Mujoomdar, BSc, PhD, Canadian Agency for Drugs and Technologies in Health, Canada; Daniel Ollendorf, PhD, Tufts Medical Center, USA; Naoko Ronquest, PhD, RTI Health Solutions, USA; Aleksandra Torbica, MSc, PhD, Bocconi University, Italy; Emily Tsiao, PharmD, Premera Blue Cross, USA; John Watkins, PharmD, MPH, BCPS, Premera Blue Cross, USA; Kai Yeung, PharmD PhD, Kaiser Permanente Washington Health Research Centre, USA.

Collaborators: Marcelo Fonseca, University of Saõ Paulo, Brazil; Carly Rodriguez, Moda Health Services, USA

References

1. Isbary G, Staab TR, Volker E, et al. Effect of crossover in oncology clinical trials on evidence levels in early benefit assessment in Germany. *Value Health*. 2017;21(6):698-706.

2. Chen G, Peirce V, Marsh W. Evaluation of the National Institute for Health and Care Excellence Diagnostics Assessment Program decisions: incremental cost-effectiveness ratio thresholds and decision-modifying factors. *Value Health*. 2020;23(10):1300-1306.

3. Boucaud-Maitre D, Berdai D, Salvo F. Added therapeutic value of medicinal products for French and German health technology assessment organizations: a systematic comparison. *Value Health*. 2021;24(3):346-352.

4. Akehurst RL, Abadie E, Renaudin N, Sarkozy F. Variation in health technology assessment and reimbursement processes in Europe. 2017. *Value Health*. 2021;20(1):67-76.

5. Drummond MF, Augustovski F, Bhattacharyya D, et al. Challenges of health technology assessment in pluralistic healthcare systems: an ISPOR Council Report. *Value Health*. 2022;25(8):1257-1267.

6. Whittington MD, Pearson SD, Rind DM, Campbell JD. The cost-effectiveness of remdesivir for hospitalized patients with COVID-19. *Value Health*. 2022;25(5):744-750.

RESEARCH ROUNDUP

Section Editor: **Aakash Bipin Gandhi, BPharm, PhD**, Research Scientist, RWE, Sanofi, Cambridge, MA, USA

Inclusion in health technology assessments: the first step toward equity.

Frank L, Concannon TW. *Health Affairs Blog*. November 10, 2021.

Summary

This piece discusses the inclusion of equity considerations in health technology assessments (HTAs). Importantly, the role of quality-adjusted life years (QALYs) in HTAs and ethical concerns regarding their impact on equity considerations are discussed in detail. For example, individuals with lived experiences (ie, chronically ill, disabled, or older adult populations) usually are not recruited for surveys that guide QALY-based HTAs. This is due to the assumption that individuals with lived experiences may overstate the value of interventions that they may receive for their care. Currently, QALYs depend on societal-level experiences and associated estimates to measure the value to be placed on different disease conditions and interventions. However, adopting this approach may understate utility estimates stated by those with lived experiences. For example, societal estimates of utilities may greatly undervalue disability care.

Relevance

Significant changes in the design of HTAs, including addressing exclusion of key populations, accounting for societal-level biases, and taking steps to tackle structural racism are required to address inequities in healthcare. Collecting the perspectives of all patients, including those with lived experiences, will help provide a comprehensive and unbiased estimate of the value they place on disease conditions, interventions, and healthcare outcomes.

An equity framework for health technology assessments.

Culyer AJ, Bombard Y. *Medical Decision Making*. 2012;32(3):428-441.

Summary

The present study discusses the importance of considering equity criteria while framing HTAs and proposes a checklist of equity items that decision makers should consider in HTAs. These items include but are not limited to addressing institutional bias, implicit stereotyping, equity-related consequences of categorizing individuals into subgroups, and accounting for legal obligations related to discrimination on the grounds of race/ethnicity, age, gender, disability, nationality, language, and sexual orientation. While the framework is not intended to be considered as a standard in the field, it has been designed with the objective of taking the first step towards guiding healthcare decision makers to prioritize a list of equity components that they should consider incorporating within HTAs. The framework proposed in this article can also complement existing equity frameworks or aid an organization's auditing processes that ensure the inclusion of equity considerations within HTAs.

Relevance

Frameworks and checklists proposed in the present article can provide a systematic and comprehensive capture of equity items that healthcare planners can consider to be included in HTAs.

Assessments of the value of new interventions should include health equity impact.

Jansen JP, Trikalinos TA, Phillips KA. *PharmacoEconomics*. 2022;40(5): 489-495

Summary

This study discusses the formal health equity impact of a new intervention for Alzheimer's disease, aducanumab, which was recently approved by the United States Food and Drug Administration. Despite its recent approval and consequent lack in availability of supporting data, the authors propose a distributional cost-effectiveness approach to quantify its health equity impact. The authors find that relative to standard of care, aducanumab can increase overall health when priced at $10,000 per year. However, there would be an increase in inequity for health outcomes when considering subgroups defined by race/ethnicity.

Relevance

Quantitative assessments of the impact of new interventions on health equity can help healthcare planners make better coverage decisions, improve program designs, and develop quality initiatives targeted at the entire population without excluding any key subgroups. Further, limited participation of racial and ethnic minorities in clinical trials associated with drug approval (such as in the case of aducanumab to treat Alzheimer's disease) does not preclude quantitative assessments related to health equity in these populations. Quantifying uncertainties associated with the health equity of an existing intervention can help facilitate its fair pricing and guide future research priorities. Population-level decision making with the objective of improving total health requires regular assessments of health equity impact of new treatments.

Note from the Section Editor: *Views, thoughts, and opinions expressed in this section are my own and not those of any organization, committee, group, or individual that I am affiliated with.*

ISPOR Conferences and Events

Virtual ISPOR Asia Pacific Summit 2022 | 20-21 September

Registration is open for the Virtual ISPOR Asia Pacific Summit 2022, the leading health economics and outcomes research (HEOR) event in the region. The summit, presented in Korea Standard Time (KST), will feature content focusing on in-depth research and discussion of the current state of HEOR in the region, and how HEOR can support health systems confronting practical issues associated with healthcare quality, access, and affordability, and finding potential solutions.

Themed "Linking HEOR Research, Evidence, and Patient Needs for Decision Making in Asia Pacific," the summit will include:

- **Two thought-provoking plenary sessions:**
  - "Value or Volume: Is the APAC Region Transforming Into Value-Based Healthcare?"
  - "Digital Health Innovations: Improving Patient Outcomes and Equity in the Asia Pacific Region"

- **Breakout Sessions covering:**
  - Real-world data and real-world evidence
  - Value-based healthcare
  - Digital transformations in healthcare
  - Innovative health financing
  - Evolution of health equity and patient engagement

  and more...

Sponsorship opportunities are available. Contact the ISPOR Sales Team at exhibit@ispor.org.

More at www.ispor.org/AsiaPacific2022

Join the conversation on Twitter #ISPORAP

ISPOR Conferences and Events

Signal Series

September 27 | 11:00AM – 12:15PM EDT

"New Insights Into ATMP Valuation and Outcomes-Based Pricing Experience"

Join us for the next ***Signal*** event to gain insight into the Danish experience with advanced therapy medicinal products valuation approach and the development of an innovative outcomes-based pricing agreement between pharma and payers. Learn about the practicalities of stakeholder involvement and data requirements and overall lessons from the outcomes-based pricing agreement experience from a multistakeholder perspective.

Host:

Julia Chamova, MBA, Senior Director, Content Strategies, ISPOR, Lawrenceville, NJ, USA

Guest Speakers:

Dorthe Bartels, Senior Strategic Advisor, New Medicines, Amgros, Copenhagen, Denmark

Pia Krogsgaard Villadsen, Head, Market Access, Novartis Healthcare, Copenhagen, Denmark

Sarah Wadmann, PhD, Senior Researcher, VIVE, The Danish Center for Social Science Research, Copenhagen, Denmark

The ***Signal*** series—ISPOR's signature program—looks beyond today's linear thinking to explore topics that will shape healthcare decision making over the next decade. ***Signal*** episodes are scheduled throughout the year and feature conversations with speakers who are innovative thought leaders and change makers in both healthcare and other sectors of economy, science disciplines, and areas of human inquiry that can impact healthcare.

Learn more and register at www.ispor.org/signal-ATMP

The conversation begins on Twitter #ISPORSignal

ISPOR Conferences and Events

ISPOR Europe 2022 | 6-9 November

Austria Center Vienna, Vienna, Austria and virtual

Registration is open for ISPOR Europe 2022, the leading European conference for health economics and outcomes research (HEOR)!

Claim your badge and plan to be there for this 3-day conference that will focus on the hottest trends in global healthcare. The conference will feature short courses, plenaries, spotlight sessions, breakouts, forums, sponsored educational symposia, poster presentations, discussion groups, and an exhibit hall. The in-person registration fee includes pre- and post-conference access to content on demand!

In addition, you'll have dedicated opportunities to network in person and virtually with HEOR expert stakeholders, global thought leaders, and your peers to explore how we establish, incentivize, and share value sustainable for health systems, patients, and technology developers.

Interested in sponsoring or exhibiting at ISPOR Europe 2022? Contact the Sales Team at exhibit@ispor.org.

More at www.ispor.org/Europe2022

Chat with us on Twitter at #ISPOREurope

ISPOR Education

Virtual ISPOR Short Courses

August 16-17 | 10:00AM – 12:00PM EDT

Model Calibration in R

This course will cover the steps and decisions involved in calibrating a mathematical model in R. The course will include an overview of model calibration including the advanced approaches of Latin hypercube sampling, directed search algorithms, Bayesian calibration, and other iterative calibrations. Extensive hands-on exercises will be woven into the course syllabus.

August 31- September 1 | 10:00AM – 12:00PM EDT

Risk-Sharing/Performance-Based Arrangements for Drugs and Other Medical Products

This course will focus on the substantial interest in performance-based risk sharing arrangements, also known as value-based contracts. Issues surrounding theory and practice, including incentives and barriers, will be analyzed along with several examples of performance-based arrangements from Europe, the United States, and Australia. A hypothetical case study will be introduced and discussed in an interactive session.

September 7 | 9:00AM – 1:00PM EDT

Budget Impact Analysis I: A 6-Step Approach

The introductory course reviews both static and dynamic methods to estimate the budget impact of a new healthcare technology following ISPOR Task Force guidance. Presented will be 6 steps related to: target population; time horizon; treatment mix; drug costs; disease-related costs; and presenting budget impact.

September 19-21 | 10:00AM – 12:00PM EDT

Budget Impact Analysis II: Applications and Design Issues

This course covers the concrete application of the 6-step approach for developing budget impact analyses and provides hands-on learning with 2 different budget impact models programmed in Excel. The course will review the basics of budget impact analysis, interpretation of results, simplicity versus accuracy and face validity, and how budget impact analyses are used by payers and other decision makers. Course enrollment includes 1-day of homework support (1 hour) between two live sessions.

September 27-28 | 10:00AM – 12:00PM EDT

Pharmacoeconomic Modeling: Applications

This course will challenge participants to apply key modeling concepts using TreeAge Pro. Hands-on modeling techniques will include decision trees, Markov models, cost-effectiveness analysis, sensitivity analysis, and probabilistic sensitivity analysis. The course does not assume any prior knowledge of TreeAge, only knowledge of basic modeling concepts.

View all ISPOR Short Courses here.

ISPOR Education

ISPOR Webinars

August 9 | 12:00PM – 1:00PM EDT

Stakeholder Engagement in Value Assessment

This webinar will offer a clear understanding of how to improve stakeholders' participation and coordination in the assessment processes. Attendees will identify opportunities to strengthen patient involvement in value assessments in Latin America.

Sponsored by FIFARMA

September 7 | 10:00AM – 11:00AM EDT

Differentiating Between Patient Preferences, Patient Reported Outcomes and Patient Engagement

The webinar will define patient preferences, patient-reported outcomes and patient engagement by describing the core defining features and outlining the complementary roles that they may have in understanding what matters to patients.

September 8 | 10:00AM – 11:00AM EDT

An Introduction to Network Meta-Analysis: A Webinar by the ISPOR Statistical Methods in HEOR Special Interest Group

This webinar will focus on the terms associated with network meta-analyses (NMA), how and why different comparisons are used, and the concepts, assumptions, and limitations associated with NMA.

September 22 | 10:00AM – 11:00AM EDT

Network Meta-Analysis — Special Topics: A Webinar by the ISPOR Statistical Methods in HEOR Special Interest Group

This advanced webinar will build on lessons learned in the introductory session and will highlight when NMA is useful for decision making, including special topics such as model approaches and Bayesian analysis.

September 30 | 9:00AM – 10:00AM EDT

Fit for Local Context? Establishing or Improving Deliberative Processes for HTA

This webinar, led by HTAi-ISPOR task force co-chairs, will focus on why a joint task force was formed to develop guidance. They will present the minimum set of considerations on the use of deliberative processes in HTA (checklist) and the approach used.

View upcoming and recent webinars here.

HEOR Solutions Center | The marketplace for expertise

The HEOR Solutions Center is an online business community that connects health economics and outcomes research (HEOR) professionals with the expertise and solutions they need for their businesses and organizations. Connect with leading health research consulting firms, contract research organizations, data management providers, digital innovators, and more. Find the right solutions to meet your business needs.

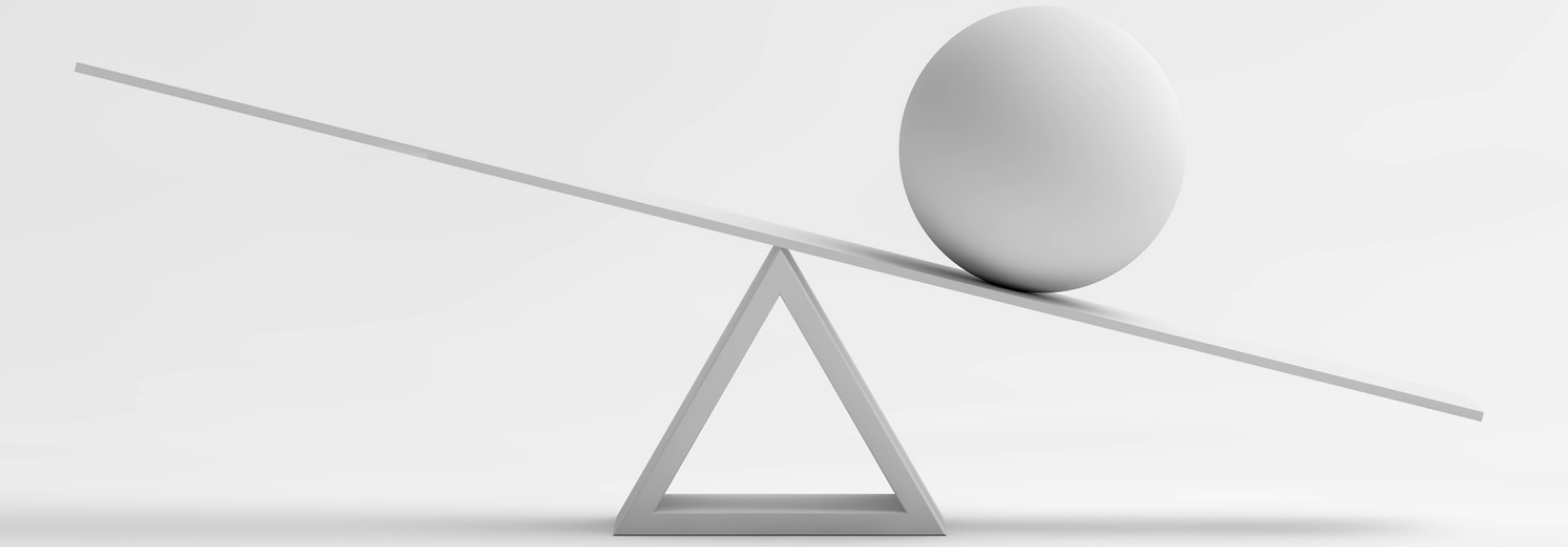
Interested in becoming an integral part of ISPOR's new online business community? For more information on joining the HEOR Solutions Center, contact exhibit@ispor.org

Details here: HEOR Solutions Center

EFFICIENCY VERSUS HEALTH EQUITY

IN HEALTH TECHNOLOGY DECISIONS

By Ilze Abersone, MS, Research Consultant,
Vital Statistics Consulting, Hoboken, NJ, USA



For decades, health technology assessment (HTA)-related decisions have almost exclusively been driven by quantitative evidence for a new technology's **efficiency**, namely its comparative- and cost-effectiveness, as well as its predicted budget impact. HTAs are used globally to inform policy makers and assist them with healthcare resource allocation decisions. However, considering efficiency alone has a potential to negatively affect **fairness**, or equity, in terms of healthcare resource distribution. One of the more recent and noticeable examples is the COVID-19 pandemic, during which numerous groups were marginalized based on their socioeconomic status or geographic location. Even today, as many Americans eagerly await the arrival of the Omicron-specific booster, there are countries where less than 10% of the population has received a primary vaccine series.

Equitable access to healthcare resources during a global pandemic has become a hot topic, where not only between-country but also *within-country* resource distribution shortcomings have been discussed. Historically, it has been the responsibility of public health professionals to develop and implement initiatives to address group-level gaps. More recently, however, health economics and outcomes research (HEOR) professionals have contributed to this matter, raising the question of whether issues of equitable healthcare resource distribution should be incorporated during HTA analyses. Would such an approach help close the ever-expanding gap of health inequity? Richard Cookson, PhD, professor at the University of York's Centre for Health

Historically, it has been the responsibility of public health professionals to develop and implement initiatives to address group-level gaps. More recently, however, HEOR professionals have contributed to this matter, raising the question of whether issues of equitable healthcare resource distribution should be incorporated during HTA analyses.

Economics in the United Kingdom, argues that it is not only doable, but believes that every cost-effectiveness analysis should be accompanied by analysis that accounts for social distribution of benefits and costs. Similarly, Mohammad Ameel, MBA, head of Primary Healthcare, Technology & Innovations in South Asia at PATH in India, points out that cost-effectiveness should only matter after a particular intervention is ensured to reach the population in need for it. Naturally, the first step in this process is to define the concept of equitable distribution and identify reasonable measurements.

The challenge of quantifying "fairness"

What gets measured—gets done (or in this case improved). Cookson emphasizes that quantification of equity is of paramount importance. "I want these numbers compared properly so that we are concerned about [equity] the same way that we are concerned about cost-effectiveness. They need to be numerically quantified so that equity issues are on the same level of playing field with other concerns." Moreover, it is not sufficient to demonstrate that there is a "small health inequality reduction" in the same way as it is not enough to suggest that a certain technology has a "small effect." Rather, the reduction in inequality must be quantified. Over the past 2 decades, the conversation of quantifying health equity alongside cost-effectiveness has gained momentum, and health economists have been working toward developing various frameworks and methodologies for effective and meaningful analyses.

"I want these numbers compared properly so that we are concerned about equity the same way that we are concerned about cost-effectiveness."
– Richard Cookson, PhD

One of the biggest roadblocks in many countries is the issue of improving data infrastructure—that is, collecting standardized sociodemographic variables that can then be readily applied in equity analyses. These are costly but invaluable undertakings; yet once these issues are resolved, the HEOR field has the analytical methodology already in place to apply these data. What Cookson refers to as a "quick and simple" distributional analysis is a relatively easy modeling method that can be built on top of an existing cost-effectiveness work. This method can provide insights in resource allocation for equity-relevant variables such as socioeconomic status, ethnicity, and geographic location. Other notable methods include multi-criteria decision analysis and weighting of willingness-to-pay thresholds in terms of disease burden.

The methods currently available are by no means perfect and are often viewed with criticism (similar to how QALYs were often disapproved of in their early years but are now used routinely). Nevertheless, they are a great starting point for understanding directionality and providing a rough estimate of the magnitude in which a new technology is advancing health equity. HEOR professionals must be careful to not tuck these results in a drawer and never look at them again, but rather to push for their implementation on a policy level.

From theory to practice

Theoretical frameworks and methodologies merely lay the groundwork but do not bring change to the table. The change happens once these frameworks are applied to real-world data and translated into action by policy makers. There are institutions, such as the National Institute for Health and Care Excellence in the United Kingdom, that are slowly starting to use distributional analyses to modify cost-effectiveness thresholds for public health guideline development. However, for now, health equity is not a standard consideration in the

majority of HTA reports. Cookson points out that they have not yet been implemented for technology appraisals because there is a mountain of legal hurdles for manufacturers along the way.

This becomes an even more far-reaching goal in many lower- and middle-income countries. Cookson and Ameel agree that in some ways, including equity in health technology appraisals for these regions is arguably more relevant than looking at cost-effectiveness. Unfortunately, there are many countries where the underlying health economics work is yet to be done before any of the more sophisticated analyses can be introduced. Ameel points out that in the South Asia region the HTA implementation is very patchy. "Countries like Thailand have very good [HTA] implementation. In India and Indonesia, it is somewhat average, but in countries like Nepal and Bangladesh, they are yet to begin health technology assessments", he explains.

> Theoretical frameworks and methodologies merely lay the groundwork but do not bring change to the table. The change happens once these frameworks are applied to real-world data and translated into action by policy makers.

Even if cost-effectiveness analyses are conducted, they are often underutilized. Ameel emphasizes that the reason why Thailand has been more successful than other southeast Asian countries in implementing HTAs in their decision making is because HTAs in the region have been institutionalized. HTAs have, similar to the case in the United Kingdom and many other countries, become part of the policy-making process. In fact, there are international research teams being created in many lower- and middle-income countries that extend cost-effectiveness analyses to consider equity-related measures, but as Cookson points out, this practice is not routine nor widespread. Furthermore, complicated political climates and lack of universal health coverage often affect the level to which such analyses are taken into account in the decision-making process.

Tradeoffs between efficiency and fairness

The question of how equity and cost-effectiveness weights should be distributed is not an easy one to answer. It seems inevitable that efficiency of a new health technology is always going to remain at the forefront of decision making. Ultimately, Cookson explains that including health equity measures in health technology appraisals is about shifting the priorities of manufacturer's research and development (R&D) teams to account for the perspective of equity-efficiency tradeoff. The overarching goal is to evaluate whether a potential technology that is highly cost-effective is going to increase or decrease health inequality if it gets funded. For example, in a world where efficiency alone dictates decision making, a borderline cost-effective, late-stage cancer treatment technology that is likely accessible only to those of higher socioeconomic status might seem more appealing to the R&D teams. However, if decision makers decided to push for investments in treatments for illnesses that are less cost-effective but are disproportionately harming marginalized populations (such as diabetes), that would greatly reduce lifetime health inequalities among certain sociodemographic groups.

Additionally, Cookson suggests that special recommendations for preventive care coverage and delivery among hard-to-reach groups, something that currently lies on the shoulders of public health and primary care professionals, should be included as part of HTAs to make equity-sensitive decisions early on. It is not easy to determine the extent to which inclusion of equity in HTA is going to reduce the health disparities, but both Ameel and Cookson strongly believe that without it, the gaps in access to healthcare resources will continue to grow.

We're slowly moving in the right direction

The COVID-19 pandemic exposed some of the major challenges communities of lower sociodemographic status experienced in accessing healthcare resources. While equity is clearly a multifold phenomenon and cannot be solved solely through its inclusion in HTAs, addressing these issues prior to a new technology's entering the market might help reduce these disparities. In some cases, we already see the equity-efficiency tradeoff in action. For example, some treatments for hepatitis C are highly cost-effective yet require large overall spending in terms of the total healthcare budget. However, since these treatments reduce overall health inequity, funding for them tends to be more generous than we would expect in a world where only budgetary issues mattered. So, it appears that we're on the right track.

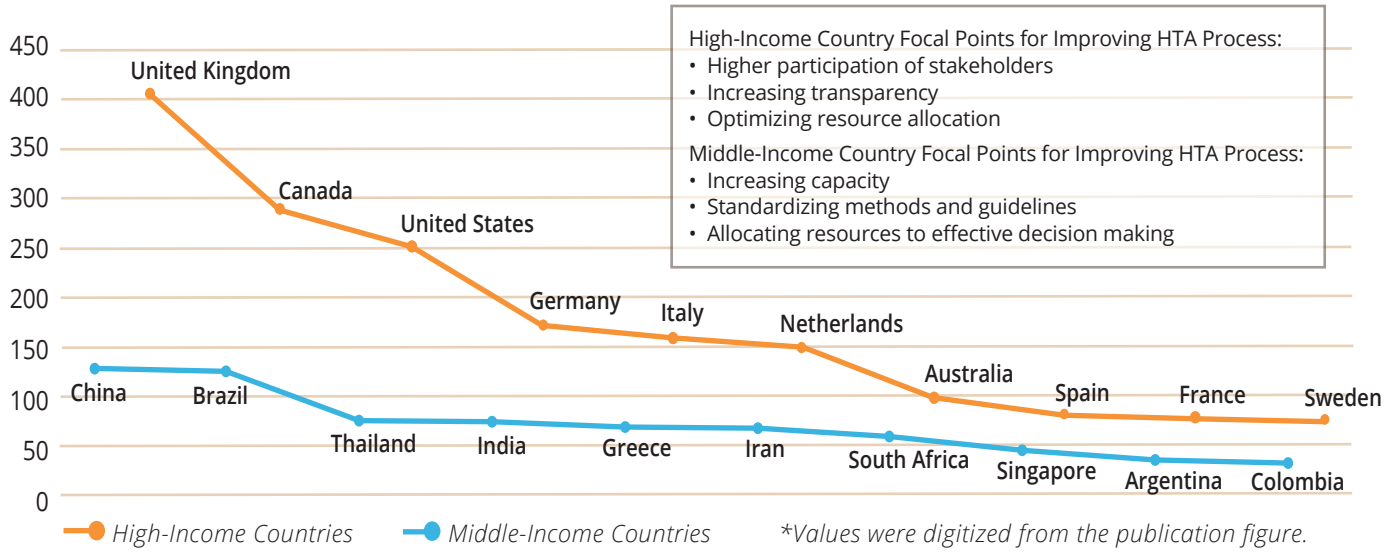
> It is not easy to determine the extent to which inclusion of equity in HTA is going to reduce the health disparities, but without it, the gaps in access to healthcare resources will continue to grow.

HTA is one of the most important tools that many policy makers around the world use to drive decisions about healthcare resource allocation. Including equity-sensitive measures in early stages of assessment therefore seems paramount, as it would not only spotlight an important issue but also allow for more nuanced formulations of future research questions in the context of technology implementation. Cookson and Ameel argue that all cost-effectiveness analyses should incorporate equity. Overall, the outlook of the experts remains positive, and while it may take time to fully implement equity measures in routine HTAs, it is likely that it will gradually happen and the ever-expanding gap of health inequality will begin to shrink.

By the Numbers: Improving Health Equity Through HTA

Section Editor: **The ISPOR Student Network**
Contributors: **Tyler D. Wagner**, Virginia Commonwealth University, Richmond, VA, USA; **Ingrid A. Cox**, University of Tasmania, Hobart, Australia; **Jacinda Tran**, University of Washington, Seattle, USA; **Jeanne Dulie Tchomchue Kom**, University of North Texas, Denton, TX, USA; **Anu Bompelli**, University of Minnesota, Minneapolis, MN, USA; **Kanya Shah**, University of Illinois at Chicago, Chicago, IL, USA

Published HTA Documents and Focal Points for Improvement by High- & Middle-Income Countries (Number of Published Documents between 2009 and 2020*)



4 categories of health equity measures in several Medicaid programs

1. Stratification of existing process, outcome, and experience measures (eg, colorectal cancer screening, childhood immunization status)
2. Direct measures of social needs and social determinants of health (eg, social needs screening and referral, access to community health workers)
3. Summary indices (eg, health equity metric, health equity summary score)
4. Measures of community well-being or deprivation (eg, area deprivation index, Hispanic health risk index)

7 principles to take into account when using quality indicators

- Indicators have to be fit for purpose
- Quality of measurement depends on quality of data and indicators
- Quality measurement has limits
- Outcome measures require risk adjustment
- Composite indicators improve simplicity but may be misleading
- A league table raises interest but is not always fair
- Be aware of gaming and unintended consequences

Understanding Value: Manufacturers' Perspectives

Editor's note: This is part 5 of a series exploring what value means to the stakeholders in healthcare. Part 1, "Expanding the Value Conversation," appeared in the May/June 2021 issue, part 2, "Understanding Value in Cancer Care," appeared in the July/August 2021 issue, part 3, "Understanding Value: The Providers' Perspective," appeared in the November/December 2021 issue, and part 4, "Understanding Value: Patients' Perspectives," appeared in the March/April 2022 issue.

About the Author

John Watkins, PharmD, MPH, BCPS, Premera Blue Cross, Mountlake Terrace, WA, USA

Today's pharmaceutical manufacturers must demonstrate the value of their products to multiple audiences. Larger companies have internal health outcomes departments whose experts develop value proposition statements for the various stakeholder groups. Smaller companies that lack internal outcomes teams can hire consultants to do the work. As we have seen in previous articles in this series, stakeholder groups have diverse overlapping perceptions of healthcare value: health economists think of it as incremental cost utility; providers see it from the point of care; and patients experience it in the realities of daily life with their diseases. Certain elements are lacking in each stakeholder's perspective. To promote more holistic value determinations, an ISPOR Special Task Force has identified additional domains that are important to various audiences and could be added to existing value frameworks.[1]

Value to a variety of audiences

If a new drug is to succeed, the manufacturer must demonstrate its value to different audiences as it progresses through the product lifecycle. Unless investors expect a reasonable return on a product in preclinical development, it will never get beyond the laboratory. The product development team must then convince clinical investigators and volunteer patients to participate in a series of trials. Investigators want publishable results with positive outcomes. Study patients hope for a cure, or at least an improvement over standard treatment options. Some trial participants value the hope that the results will benefit future patients with the same disease. Throughout the process, corporate decision makers must continue believing that the drug's prospects justify development costs.

When the trials are completed, the manufacturer must convince the US Food and Drug Administration (FDA) that their product is *efficacious* (reasonably likely to benefit patients) and *safe* (unlikely to cause offsetting harm). In the interest of making beneficial treatments available to patients as soon as possible, regulators often accept intermediate endpoints from short-term trials. These intermediates may be insufficient to convince payers, providers, and patients that the drug will produce meaningful clinical outcomes, but this practical compromise balances rapid access to the drug with assurance of its real effectiveness. In any case, the data should be the primary rationale for FDA approval, but it is the manufacturer's responsibility to ensure that it is packaged correctly to avoid misinterpretation.

Payers want more robust evidence of value. For chronic diseases, this requires longer trials with real clinical endpoints. Some payers require models of cost-effectiveness and affordability. In determining coverage policy, payers may seek to limit use to patient subgroups for whom the evidence predicts greater net benefit. Providers may be less concerned with budget and cost-effectiveness analysis, but they too want to see real clinical outcomes that bring value to patients and achieve their clinical goals. They value improvements in therapy that save time and improve their workflow and productivity and that of their office staff.

In the absence of a cure, patients with chronic disease want to live longer, improve quality of life, and maintain the ability to function in roles that are important to them. Value to patients is very personal. Surveys of patient groups with the same disease provide aggregate overviews, but only the individual can say what matters most. Robust dialogue with patient representatives should begin early in the drug development process and continue through launch and beyond. Based on a literature review, Cook et al concluded that, "Companies who embrace the involvement of patients in early product development, prior to beginning pivotal clinical trials, are most likely to ensure a fit of their products to the real needs of the patients and provide the therapeutic outcomes they are looking for."[2]

Payers and providers want to know how well a drug will work outside of a controlled trial setting—in the real world, where protocols are not strictly followed and patients don't always take their medicine or follow medical advice. Real-world patients may differ from those in the clinical trials, which exclude complex patients to reduce the likelihood of confounding. Real-world observational studies can help answer these questions, and most manufacturers are willing to sponsor these studies. Using a drug in patients expected to respond well to treatment will improve providers' perceptions of its value.

Value shaped by those they serve

Manufacturers have their own perceptions of value apart from what they present to their external audiences. A manufacturer's definition of value affects their approach to drug development, the diseases they target, and the types of drugs they choose to research. "Our perspective on value in healthcare focuses on treatments," says Patrick Holmes, MS, Science and Innovation Policy Team Lead at Pfizer. "We are committed to advancing medicines wherever we believe we can make a meaningful difference for patients." With their extensive resources, most large companies like Pfizer simultaneously develop a variety of products that target a broad range of diseases. Small companies generally have a narrower focus. For example, Pfizer's Comirnaty mRNA COVID vaccine is just one of many products launched since 2020 that are making a difference for patients, while its major competitor, Moderna's Spikevax, is the company's only commercialized product, although they have other mRNA vaccines in various stages of development.[3]

Phillip Buck, senior director, Health Economics and Outcomes Research at Moderna, believes that value is "rapid implementation of innovative healthcare interventions, including safe and effective vaccines and transformative medicines that contribute to improved real-world public health outcomes and represent good value-for-money." The public health focus of this vision statement aptly describes Moderna's mRNA platform, whose salient characteristic is its agility, the ability to quickly develop vaccine for a new virus, and rapidly produce large quantities for mass vaccination.

The same could be said of Comirnaty, but Pfizer's vision reflects the variety of its products and patient populations. It is both broad and specific, as Holmes explains: "The value of a treatment always starts with the clinical benefit it provides to patients…the degree to which a treatment mitigates or solves the medical condition that the patient has been diagnosed with and for which the treatment has been selected." It is more than that, he continues. It also encompasses "other considerations, such as how a treatment affects a patient's family, social life, and ability to work." His definition includes "how healthcare providers view the treatment in the context of its benefits and risks. Providers are closest to patients, so their perception of the value of a treatment is critical."

To complete the holistic picture, Holmes explains, "Value also includes layers further from patients, such as the impact of a treatment for employers, insurers, and manufacturers. From our perspective, these viewpoints are important to capturing the full value of a treatment but should be considered secondarily to the benefits of the treatment to patients." It also incorporates "societal and humanistic elements (eg, reduced caregiver burden, peace of mind, health equity, and reduced fear of contagion)."

Genentech's Elaine Yu, PharmD, MS, head of Evidence for Access Oncology, includes all of the above in her definition of value, plus total treatment cost. In some cases, an expensive drug may greatly reduce other costs, offsetting the drug's price. But with others, such as CAR T-cell therapy, the concomitant costs can almost double the already high drug price. "At Genentech, we aim to reduce total cost of care whenever possible," Yu says. Genentech's aim in pursuing value in cancer care is threefold: improving patient outcomes, helping patients maintain or improve health-related quality of life, and maximizing gains to society.[4]

Value perceived as unmet need

Unmet need has always been a key factor driving pharmaceutical research and guiding its direction. Assessment of need should be a realistic measurement of the gap between current standard of care and the ideal state, devoid of wishful thinking. Greater unmet need predicts more demand for a product that addresses that need. It is relatively easy to identify need and to estimate the number of target patients with the need, but more difficult to predict the extent to which the proposed treatment will actually fill the gap that has been identified. The manufacturer must make the decision to move the product forward in testing without knowing how well it will meet the need. As a senior outcomes leader at a large biotechnology drug manufacturer explains, "The value of a new technology is always relative to the existing standard of care for the disease of interest. New drugs do not have value in a vacuum; they have value relative to the next best alternative."

"Patients may quantify value in a very different way, compared to a payer or a health economist," he observes. "They might rank safety much higher. They might attribute more value to immediate improvements in quality of life, relative to theoretical improvements in long-term survival." Because the FDA does not require head-to-head trials "relative to an existing standard of care, it becomes very difficult to assess an incremental value. The system as a whole could do a better job at weeding out drugs with low or zero value earlier in the development process."

> "The value of a treatment always starts with the clinical benefit it provides to patients' the degree to which a treatment mitigates or solves the medical condition that the patient has been diagnosed with and for which the treatment has been selected." – Patrick Holmes, MS

The importance of achieving success for a new product biases the development team toward an optimistic outlook. As with one's children, it is easy focus on positive qualities and overlook shortcomings, so that, when a product reaches market, the manufacturer is surprised at its lukewarm reception. Seeking input from patients, physicians, and payers throughout the development process will avoid this situation, since development can be halted before the large investment required to stage late phase clinical trials.

Gene therapy and other cutting-edge treatments may cure diseases that have always been chronic, lifelong conditions. The broader term "transformative" characterizes treatments that may not actually cure, but may halt or radically alter the progression of a chronic disease, a goal which for Novartis is an integral part of their strategic vision. "In our pursuit of transformative treatments, we challenge medical paradigms and explore possibilities to cure disease, intervene earlier in chronic illnesses, and find ways to dramatically improve quality of life."[5] More attention to finding cures addresses major unmet needs and could balance the strategy of prioritizing maintenance medications for chronic diseases, an approach that made business sense, but as the COVID pandemic demonstrated, has taken resources from the development of vaccines and antiviral drugs.

Value addressing healthcare disparities

As we become more aware of how our healthcare system has overlooked racial and ethnic minorities and other underserved groups, many manufacturers are seeking to expand diversity in clinical trial populations and increase applicability of results to minority patients. The Beacon of Hope project is taking concrete steps to change this. "Health disparities affecting minority groups are endemic in the United States. Compared with non-Hispanic Whites, Blacks/African Americans have a lower life expectancy, a higher mortality rate from cancer, a dramatically

greater likelihood of diseases such as asthma, and significantly increased rates of infant mortality," according to the project's Web page. Vaccine hesitancy during the COVID pandemic has revealed the extent of minority groups' distrust in the system that further increases disparities in care. The project is working with historically Black colleges and universities to improve education of the next generation of Black professionals, support the development of digitally enabled clinical trial centers that will increase enrollment of patients of color, support research and validation of existing standards that drive diagnosis and clinical practice guidelines to ensure fairness to minorities, and address climate and environmental factors that exacerbate health disparities for minorities.[6]

Other manufacturers are encouraged to join Novartis in the Beacon of Hope project. "Merck is proud to participate in a collaboration focused on improving enrollment of underrepresented people into clinical trials with the common goal of ensuring these trials appropriately reflect the diversity of the patients we serve worldwide," notes Andy Lee, Head of Global Clinical Trial Operations at Merck.[7] Sanofi has joined the project as well. "To make sure all patients can benefit from our medicines, we must understand how these medicines work in diverse populations, especially in groups that have been historically underrepresented in clinical trials," explains Dietmar Berger, MD, chief medical officer, Global Head of Development at Sanofi.[8]

Efforts to reduce disparities are not limited to developed countries. The Access to Medicines Foundation, an independent nonprofit organization based in The Netherlands, "aims to advance access to medicine in low- and middle-income countries by stimulating and guiding the pharmaceutical industry to play a greater role in improving access." The Foundation publishes an annual index of major manufacturers, ranking them based on their efforts in this area. The 2021 index top 10 companies were, in order, GlaxoSmithKline, Novartis, Johnson & Johnson, Pfizer, Sanofi, Takeda, AstraZeneca, Merck, Roche, and Novo Nordisk.[9]

Value of small companies entering the market

A number of small companies with innovative technologies or products are entering the market, targeting rare diseases, such as spinal muscular atrophy, which was featured in a previous article. The gene therapy for this disease was developed by AveXis pharmaceuticals. Companies like this will be an important part of healthcare's future.

Not all small companies are innovators. Some companies sell branded versions of older drugs, with enhancements that seldom offer sufficient incremental benefit to justify the substantially higher price. These companies can be distinguished by the value proposition stated on the company's website, whether it is specific and detailed. Less innovative companies usually describe their value in vague generalities.

Summary

As with the stakeholder groups featured in previous articles, there is a great deal of variation among pharmaceutical manufacturers. Companies vary in size, culture, vision, country of origin, customer base, and other characteristics. Because they have to articulate their value to multiple audiences, most manufacturers have thought about it from different perspectives and received feedback from their audiences. Thus, they are more likely to be self-aware, having thought extensively about their place in healthcare.

Like all of us, manufacturers have "blind spots" in their vision. They tend to focus on value to the patients treated with their drugs, believing that this value justifies the high prices of their products. In doing so, they may ignore the marginal costs to society. As healthcare CEO Vivian Lee explains, "Companies that cover employee health insurance have seen rising costs erode their margins and hobble competitiveness. Much of that ever-rising expense has been passed on to employees, often in hidden ways like flat wages over the past 50 years…Healthcare is bankrupting the uninsured and…it's often disappointing the millions who do have coverage."[10] Because of the high cost of healthcare, American workers lose jobs to automation or to countries where employees cost less, and the cost of health insurance is not borne by employers. Like other players in healthcare, manufacturers are not solely responsible for this, but they must acknowledge their role in escalating healthcare costs, a problem we must all work together to solve.

References

1. Lakdawalla DN, Joshi JA, Garrison LP, et al. Defining elements of value in health care-a health economics approach: an ISPOR Special Task Force Report 3. *Value Health*. 2018 Feb;21(2):131-139.

2. Cook NS, Cave J, Holtorf AP. Patient preference studies during early drug development: aligning stakeholders to ensure development plans meet patient needs. *Front Med* (Lausanne). 2019 Apr 24;6:82. doi:10.3389/fmed.2019.00082. eCollection 2019.

3. Moderna. Research Pipeline Products. Accessed July 1, 2022. https://www.modernatx.com/research/product-pipeline

4. Yu E. Value in Cancer Care: Accounting for What Really Matters. Accessed July 5, 2022. https://www.gene.com/stories/value-in-cancer-care-accounting-for-what-really-matters?topic=economic-sustainability-in-cancer-care

5. Novartis Pharmaceuticals. Strategic Priorities. Accessed July 2, 2022. https://www.novartis.com/about/strategy

6. Novartis Pharmaceuticals. Beacon of Hope: Addressing health disparities through holistic community-based collective action. Accessed July 2, 2022. https://www.novartis.com/news/beacon-hope-addressing-health-disparities-through-holistic-community-based-collective-action

7. Merck Pharmaceuticals. Merck joins Beacon of Hope to increase diversity in clinical trials. Accessed July 2, 2022. https://www.merck.com/stories/merck-joins-beacon-of-hope-to-increase-diversity-in-clinical-trials/

8. Novartis Pharmaceuticals. Novartis expands Beacon of Hope through alliances with historically Black medical schools to address systemic health disparities. Accessed July 2, 2022. https://www.prnewswire.com/news-releases/novartis-expands-beacon-of-hope-through-alliances-with-historically-black-medical-schools-to-address-systemic-health-disparities-301572503.html

9. Access to Medicine Foundation. Access to Medicine Index 2021. Accessed July 2, 2022. https://accesstomedicinefoundation.org/media/uploads/downloads/613f5fb390319_Access_to_Medicine_Index_2021.pdf

10. Lee VS. *The Long Fix: Solving America's Health Care Crisis with Strategies That Work for Everyone*. New York, NY: WW Norton & Company; 2020.

Addressing Health Inequity in Value Assessments: A New Role for HEOR?

Richard Z. Xie, PhD, The Innovation and Value Initiative, Alexandria, VA, USA; **Susan dosReis, PhD**, University of Maryland School of Pharmacy, Baltimore, MD, USA; **Stacey Kowal, MSc**, Genentech, Alameda, CA, USA; **Louis P. Garrison, PhD**, The Comparative Health Outcomes, Policy, and Economics (CHOICE) Institute, University of Washington, Seattle, WA, USA

Ensure more representative data inputs are captured, especially from underrepresented communities.

Consider not only the population-level average impact of a health intervention, but also the equity impacts on different subgroups, using tools such as distributional cost-effective analysis.

Develop pricing frameworks that can better serve the needs of diverse subpopulations and health systems.

Introduction

While the specific terminology varies by discipline and country (eg, "health disparities" in the United States, "health inequalities" in the United Kingdom), unjustifiable differences in health, healthcare access and use, and financial protection from healthcare costs among different segments of society have been widely documented across diseases and regions.[1-3] The lack of attention to equity considerations has been brought home with the COVID-19 pandemic and calls are increasingly being made to incorporate equity considerations in health-related decision making (eg, in coverage decisions).[1,4,5] As a result, the health economics and outcomes research (HEOR) community has recognized our important role in generating key insights, providing data and analytic frameworks that can inform these important decisions.

In May 2021, the Innovation and Value Initiative (IVI) hosted a workshop at the ISPOR Annual Meeting to discuss key considerations and showcase novel methods the HEOR community can leverage to support the consideration of health equity in healthcare decision making. This article summarizes important takeaways from the workshop and provides practical suggestions including (1) ensuring that more representative data inputs are captured, especially from underrepresented communities, (2) considering not only the population-level average impact of a health intervention, but also the equity impacts on different subgroups using tools such as distributional cost-effective analysis, (DCEA), and (3) developing pricing frameworks that can better serve the needs of diverse subpopulations and countries.

Ensuring more representative data inputs are captured

A representative sample of the target patient population is a necessary first step toward understanding health and healthcare disparities. Accounting for patient heterogeneity across people of varying race, ethnicity, and socioeconomic status enables a more comprehensive understanding of patient perspectives, needs, and values. Failure to do so may result in biased findings and healthcare decisions that perpetuate existing systemic disparities.[6,7]

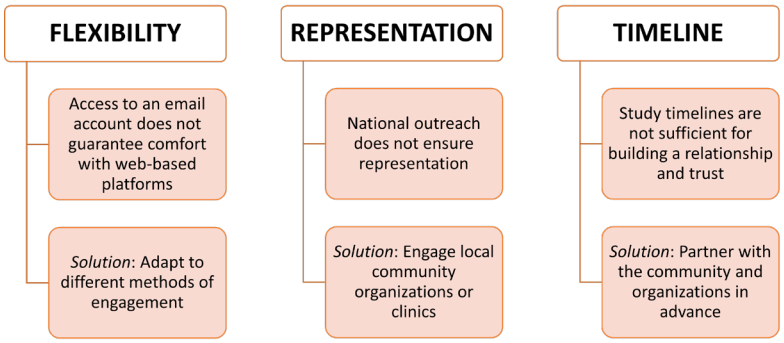
> The lack of attention to equity considerations has been brought home with the COVID-19 pandemic and calls are increasingly being made to incorporate equity considerations in health-related decision making.

Patient heterogeneity in preferences for healthcare services and interventions is an important focus of the Patient-Driven Values in Healthcare Evaluation (PAVE) Center at the University of Maryland School of Pharmacy. Through a stakeholder-engaged process, PAVE Center researchers incorporate stated preference methods such as discrete choice experiments (DCE) to quantify preference heterogeneity across diverse patient groups.[8] Using the PAVE patient-informed value element conceptual model,[9] researchers identify value elements (eg, length of treatment, side effects, ability to work) that are prioritized by patients for a given medical condition, and then operationalize these in a quantitative instrument that allows the relative importance of each element to be estimated, stratified by diversity subgroups.[10] Subsequently, these insights and findings can be incorporated into methods used to inform health technology assessment, such as economic modeling.

For prospective data collection efforts like the PAVE approach to be successful, ensuring participation from historically underrepresented patient subgroups (eg,

those from racial/ethnic minority groups or rural areas) is key. To encourage participation from underrepresented subgroups, researchers should engage with communities of these subgroups and/or healthcare facilities serving these communities before study inception and throughout different study phases. Researchers should make a deliberate effort to understand the barriers (eg, health literacy) to participation from underrepresented patient groups, build trust with community members, and use different engagement and survey methods based on the needs of local communities (**Figure 1**).

Figure 1. Key Considerations in Overcoming Barriers to Recruiting Representative Patient Samples

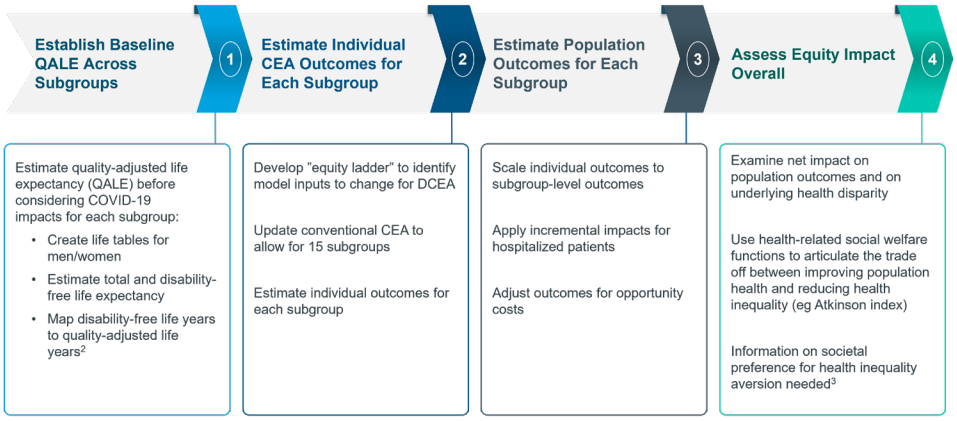


Considering population-level impact of a health intervention and the equity impacts on different subgroups

The cost-effectiveness analysis (CEA) is commonly used as a population-level decision tool to inform resource allocation efficiently within a limited budget. However, existing CEA models seek to maximize efficiency by achieving the largest overall gains in health for a given cost and population of interest. However, even if a healthcare intervention is cost-effective at a population level, health and cost outcomes can vary among different population segments depending on various factors, including underlying health risks, uptake, capability to benefit, and, importantly, who will bear the opportunity costs of diverting scarce resources from other uses.[6,11]

DCEA, an extension of CEA most commonly used outside the United States, allows the comparative valuation of therapeutic alternatives to consider dual objectives, quantifying and comparing tradeoffs between overall gains in health against underlying impacts on health equity.[11,12] In an ongoing study, researchers from Genentech demonstrated how the DCEA approach could be implemented in the US setting through a pilot application that examined how the funding of COVID-19 inpatient treatments may impact underlying health disparities.[a,13] **Figure 2** offers a topline view of the DCEA process implementation based on this specific example. The 4 key steps

Figure 2. Topline View of the DCEA Process



1. Cookson R, Griffin S, Norheim OF, Culyer AJ, editors. Distributional Cost-Effectiveness Analysis: Quantifying Health Equity Impacts and Trade-Offs. Oxford University Press; 2020 Sep 30
2. Asaria M, Griffin S, Cookson R. Distributional cost-effectiveness analysis: a tutorial. Medical Decision Making. 2016 Jan;36(1):8-19.
3. Robson M, Asaria M, Cookson R, Tsuchiya A, Ali S. Eliciting the level of health inequality aversion in England. Health economics. 2017 Oct;26(10):1328-34

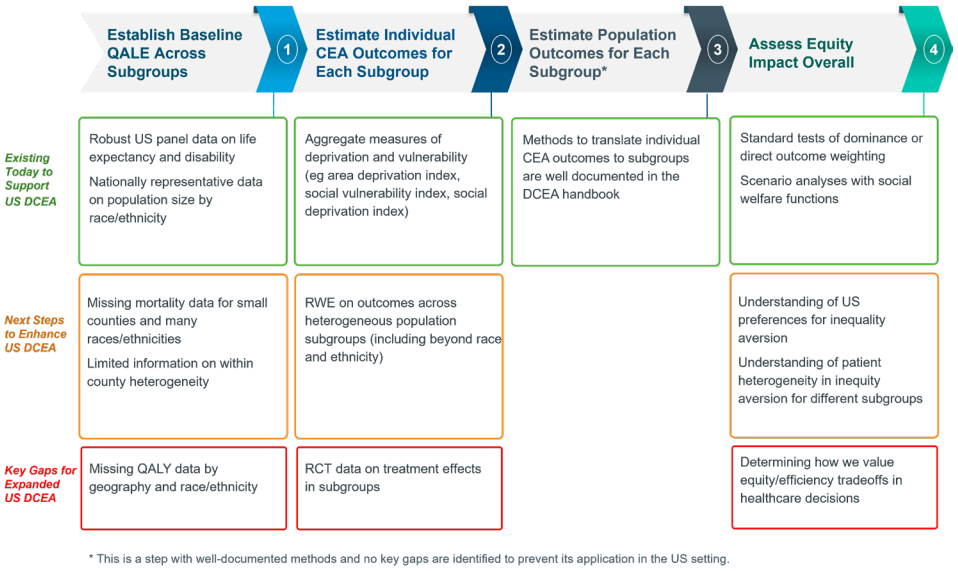
of the DCEA process are (1) estimating baseline quality-adjusted life expectancy (QALE) across different subgroups, (2) estimating individual CEA outcomes for each subgroup, (3) estimating population outcomes for each subgroup, and (4) assessing the overall equity impact.

The pilot study illustrated the mechanics and feasibility of applying a DCEA in the United States. Topline results generated important insights for decision making: (1) subgroups with higher levels of social vulnerability had higher quality-adjusted life year (QALY) gains given lower baseline health and higher baseline risk of contracting and dying from COVID-19, and (2) COVID-19 treatments were both cost-effective and had a net positive impact on health equity, given the larger relative gains for more socially vulnerable populations.

This DCEA application in the US setting demonstrated that the HEOR community in the United States could leverage existing data sources to assess the equity impacts of funding healthcare interventions. However, this work also highlighted key data gaps that need to be filled to further expand use of this approach. For example, in the second step, when researchers modeled intervention impacts on different subgroups, treatment effect data were not readily available by subgroup. So, the research team pivoted and modeled the intervention impacts on different subgroups based on real-world evidence that showed how baseline disease risks and inpatient outcomes were impacted by the level of social vulnerability, across US counties. **Figure 3** provides a summary of these data gaps.

[a] For additional details of the application, please refer to the prerelease recordings from ISPOR 2021 Annual Meeting.

Figure 3. US Data Availability and Research Priorities for DCEA



CEA indicates cost-effectiveness analysis; DCEA, distributional cost-effectiveness analysis; QALY, quality-adjusted life year; RCT, randomized controlled trial; RWE, real-world evidence; US, United States.

Developing pricing frameworks that serve the needs of diverse subpopulations and countries

While pharmaceutical[b] innovations have contributed to improved life expectancy and quality of life, we should be mindful of the equity implications of newly approved therapies.[14] Pharmaceutical innovation is potentially rewarding for patients but is often a highly risky venture for public and private investors. In recent years, driven by market incentives and the regulatory environment such as the 21 Century Cures Act, newly approved therapies have increasingly focused on severe rare disease areas with largely unmet needs.[15] For example, in 2020, 58% of new drugs approved by the Center for Drug Evaluation and Research of the US Food and Drug Administration were indicated for orphan diseases. Fewer approvals in disease areas that impact broader segments of the population, such as Alzheimer's disease, are occurring.[16,17]

In assessing pricing and reimbursement decisions for innovative medicines, value-based pricing frameworks could be adapted to incorporate equity concerns. Economists have long argued for differential pricing in access to pharmaceuticals.[18] Income and wealth differences both within the United States and elsewhere influence people's ability to pay for medicines and thus may mute investment signals to innovators as well as the overall amount available in the research and development ecosystem. Differential pricing, where novel medicines are priced according to the willingness to pay of different subpopulations, can potentially improve access and uptake. Compared with a scenario where a uniform price is set for all subpopulations, differential pricing can potentially reduce disparities within or across countries as well as support equity and dynamic efficiency from a global perspective. In fact, differential pricing is already being applied in the United States, as various insurance payers (eg, Medicare, Medicaid, commercial, and VA) often pay different prices for the same branded drug.[19] Differential pricing is, in effect, applying different cost-effectiveness thresholds—which generally affect differences in the ability to pay—for different populations and disease conditions. This redistribution promotes greater access for the less well off, thereby supporting health equity. This is not to say that observed price differences adequately address health disparities, but rather to point out that inequities are recognized, and we need to enhance our analytical and policy tools to better manage them.

To incorporate equity considerations into pricing for novel therapies, decision makers will need to clearly define equity concepts (ie, in terms of outcomes, opportunities, or processes) in specific decision contexts and then develop corresponding measures. With clearly defined equity criteria, improved data inputs and methods such as the DCEA can provide insights into the equity impacts of different alternatives and inform the pricing of novel therapies.

Conclusion

It is imperative that we tackle the widening health disparities in our society.[20–22] As members of the HEOR community, we can work with various stakeholders to take immediate action, particularly on improved data inputs and improvement of the methods that inform decision making with potential equity impacts. Promising new methods should continue to be tested and optimized to better address health disparities. In research initiatives, we can: (1) ensure more representative data inputs are captured, especially from underrepresented communities; (2) consider not only the population-level average impact of a health intervention, but the equity impacts on different subgroups using tools such as DCEA; and (3) develop pricing frameworks that can better serve the needs of diverse subpopulations and countries.

References

1. Figueroa JF, Wadhera RK, Lee D, Yeh RW, Sommers BD. Community-level factors associated with racial and ethnic disparities in COVID-19 rates in Massachusetts. *Health Aff*. Published online August 27, 2020:10.1377/hlthaff. doi:10.1377/hlthaff.2020.01040

2. Xie Z, Clair PS, Goldman DP, Joyce G. Racial and ethnic disparities in medication adherence among privately insured patients in the United States. *PLoS One*. 2019;14(2). doi:10.1371/journal.pone.0212117

3. Patel V, Burns JK, Dhingra M, Tarver L, Kohrt BA, Lund C. Income inequality and depression: a systematic review and meta-analysis of the association and a scoping review of mechanisms. *World Psychiatry*. 2018;17(1):76-89. doi:10.1002/wps.20492

4. Azar KMJ, Shen Z, Romanelli RJ, et al. Disparities in outcomes among COVID-19 patients in a large health care system in California. *Health Aff*. 2020;39(7):1253-1262. doi:10.1377/hlthaff.2020.00598

[b] The analytic framework in this section also applies to other types of innovations in healthcare such as nonpharmaceutical products.

5. Czeisler MÉ, Lane RI, Petrosky E, et al. Mental health, substance use, and suicidal ideation during the COVID-19 pandemic—United States, June 24–30, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(32):1049-1057. doi:10.15585/mmwr.mm6932a1

6. Ramaekers BLT, Joore MA, Grutters JPC. How should we deal with patient heterogeneity in economic evaluation: a systematic review of national pharmacoeconomic guidelines. *Value Health*. 2013;16(5):855-862. doi:10.1016/j.jval.2013.02.013

7. Willke RJ, Neumann PJ, Garrison LP, Ramsey SD. Review of recent US value frameworks-a health economics approach: an ISPOR Special Task Force Report [6]. 2018;21(2):155-160. https://doi.org/10.1016/j.jval.2017.12.011

8. Zhou M, Bridges JFP. Explore preference heterogeneity for treatment among people with type 2 diabetes: a comparison of random-parameters and latent-class estimation techniques. *J Choice Model*. 2019;30:38-49. doi:10.1016/j.jocm.2018.11.002

9. dosReis S, Butler B, Caicedo J, et al. Stakeholder-engaged derivation of patient-informed value elements. *Patient*. 2020;13(5):611-621. doi:10.1007/s40271-020-00433-8

10. Slejko JF, Hong YD, Sullivan JL, Reed RM, dosReis S. Prioritization and refinement of patient-informed value elements as attributes for chronic obstructive pulmonary disease treatment preferences. *Patient*. 2021;14(5):569-579. doi:10.1007/s40271-021-00495-2

11. Cookson R, Griffin S, Norheim OF, Culyer AJ. Distributional Cost-Effectiveness Analysis: *Quantifying Health Equity Impacts and Trade-Offs*. Oxford University Press; 2020. doi:10.1093/MED/9780198838197.001.0001

12. Cookson R, Griffin S, Norheim OF, Culyer AJ, Chalkidou K. Distributional cost-effectiveness analysis comes of age. *Value Health*. 2021;24(1):118-120. doi:10.1016/J.JVAL.2020.10.001

13. Kowal S, Ng C, Shuldt R, Sheinson D, Cookson R (in press). *The Impact of Funding Inpatient Treatment for COVID-19 on Health Equity in the US: A Distributional Cost-Effectiveness Analysis*. 2021.

14. Buxbaum JD, Chernew ME, Fendrick AM, Cutler DM. Contributions of public health, pharmaceuticals, and other medical care to US life expectancy changes, 1990-2015. *Health Aff*. 2020;39(9):1546-1556. doi:10.1377/hlthaff.2020.00284

15. Miller KL, Fermaglich LJ, Maynard J. Using four decades of FDA orphan drug designations to describe trends in rare disease drug development: substantial growth seen in development of drugs for rare oncologic, neurologic, and pediatric-onset diseases. *Orphanet J Rare Dis*. 2021;16(1):1-10. doi:10.1186/S13023-021-01901-6

16. Bountra C, Lee WH, Lezaun J. *A New Pharmaceutical Commons: Transforming Drug Discovery*.; 2017. Accessed February 28, 2021. https://www.oxfordmartin.ox.ac.uk/downloads/academic/Transforming_Drug_Discovery.pdf

17. Batta A, Kalra BS, Khirasaria R. Trends in FDA drug approvals over last 2 decades: an observational study. *J Fam Med Prim Care*. 2020;9(1):105. doi:10.4103/JFMPC.JFMPC_578_19

18. Danzon PM, Towse A, Mestre-Ferrandiz J. Value-based differential pricing: efficient prices for drugs in a global context. *Health Econ*. 2015;24(3):294-301. doi:10.1002/hec.3021

19. A Comparison of Brand-Name Drug Prices Among Selected Federal Programs. *Congr Budg Off Rep*. Accessed September 3, 2021. www.cbo.gov/publication/56978

20. Mahase E. A decade on from Marmot, why are health inequalities widening? *BMJ*. 2019;365:l4251. doi:10.1136/BMJ.L4251

21. Ku L, Brantley E. Widening social and health inequalities during the COVID-19 pandemic. *JAMA Heal Forum*. 2020;1(6):e200721-e200721. doi:10.1001/JAMAHEALTHFORUM.2020.0721

22. Gati SB, Bloomhardt HM, McArthur EA. COVID-19: widening health disparities among pediatric populations. *Am J Public Health*. 2020;110(9):1358-1359. doi:10.2105/AJPH.2020.305815

The Many Tentacles of Estimands in HEOR—From PROs to RWD

Jessica Roydhouse PhD, Menzies Institute for Medical Research, University of Tasmania, Hobart, TAS, Australia; **Roee Gutman PhD**, Brown University School of Public Health, Providence, RI, USA; **Pallavi Mishra-Kalyani PhD**, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, USA; **Stephanie Manson PhD**, Novartis, East Hanover, NJ, USA

Using estimands offers an important opportunity to health economists and health outcomes researchers to minimize uncertainty during study planning when estimating the effects of interventions using different data sources, from patient-reported outcomes to real-world data.

In comparative effectiveness studies, estimands also enable researchers to examine the sensitivity of the results to assumptions made during the analysis phase of a study.

Estimands: What Are They and How Are They Useful?

What is the effect of an intervention on an outcome?

Determining the effect of an intervention involves examining the causal effect of that intervention. In a hypothetical world, to compare the effects of possible interventions for each patient, we would simultaneously assign patients to all interventions, observe their outcomes for all interventions, and identify differences between these outcomes. In the real world, we are only able to assign individuals to one intervention at a time and then see their outcomes for that intervention. Thus, we cannot estimate individual-level treatment effects using this mechanism. However, we can estimate sample-level or population-level treatment effects. Formally, an *estimand* is a "precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same patients under different treatments being compared."[1] Therefore, the estimand provides a tool to address structural uncertainty in our data using preplanned analyses. In this article, we will use therapeutic studies as examples, but these issues are relevant to studies of any interventions.

Challenges in Assessing Treatment Effects

Because we cannot observe individuals under multiple interventions at the same point in time, we need to ensure that participants in all arms are similar on average to identify the effect of the intervention. Balancing participant characteristics across intervention arms is accomplished by randomization in randomized controlled trials (RCTs) and in real-world data (RWD) studies, by using procedures such as matching or weighting. In RCTs without complications, randomization supports the inference that the assigned treatment is causally related to the observed effects.

However, the clinical context of randomized or observational studies can present complications that lead to difficulties in measuring and interpreting observed effects. In studies with complications, there can be unplanned events that change the clinical course of patients. For example, patients may use a rescue medication or discontinue a medication because of lack of efficacy or because of adverse events. Such events are commonly referred to as intercurrent events. How and if these events are accounted for in the analysis can influence the understanding of the efficacy of interventions. This emphasizes the need to *a priori* construct a study design that addresses intercurrent events. Early engagement with statisticians, patients, and clinicians is important for identifying processes to address intercurrent events that may arise during the course of a study. The types of intercurrent events that may arise and the analytic strategies to address intercurrent events should be informed by the clinical context.

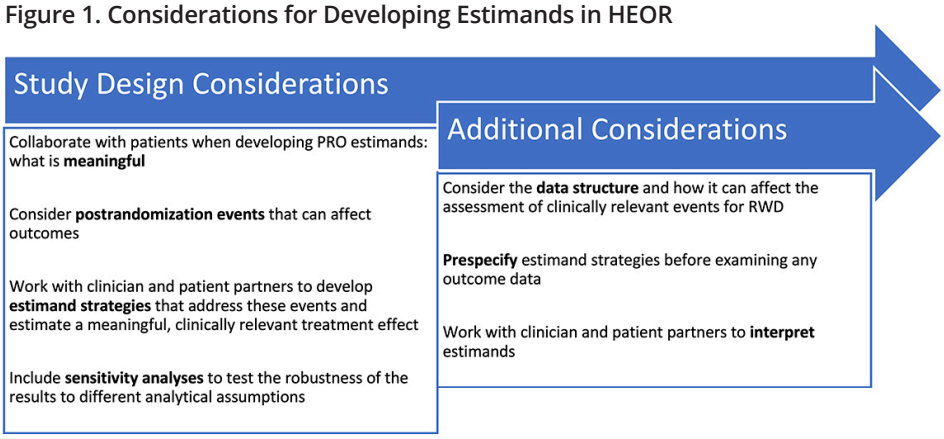
> The estimand provides a tool to address structural uncertainty in our data using preplanned analyses.

By carefully constructing study estimands, researchers can have a better understanding of the impact of interventions on the course of a disease while considering the influence of intercurrent events.

Estimands for PRO Data

Patient-centric trials are important and encouraged by regulatory agencies. Patient-reported outcomes (PROs) are one way to assess a patient's experience during a trial. Although PRO data are valuable, hypotheses and objectives for PRO data are not always clearly stated. Analyses of PRO data are sometimes inconsistent in how they address intercurrent events that arise during the course of the trial.[2] Considering PRO data in the context of postrandomization,

Figure 1. Considerations for Developing Estimands in HEOR



HEOR indicates health economics and outcomes research; PRO, patient-reported outcomes; RWD, real-world data.

events can be useful in providing more encompassing information on the effect of interventions. For example, in oncology and other trials, patients may stop treatment and/or stop providing PRO data for many reasons, including death, disease progression, or intolerable drug side effects. There may be clinically relevant reasons to incorporate these events in a trial's analytic strategy and overall design in different ways.

There may also be other events that can affect PRO endpoints that are important to consider. Consider a PRO endpoint of change from baseline in pain severity in a trial comparing 2 pain-relieving medications. It would be unethical to not allow the use of medications other than the trial medication, even if the use of those medications may improve patients' pain and influence the endpoint. There are several possible estimands for estimating a treatment effect that consider this challenge. One would be to look at what would have happened in a hypothetical or imagined scenario where no additional medications were allowed. This estimand is usually modeled because it is hypothetical, and some patients are only observed while taking the additional medication. However, modeling can provide important information about the effect of treatment under different plausible scenarios. Another option would be to include PRO data only up to the point a nontrial medication is used while ensuring that assumptions based on randomization are not violated. A different estimand would examine the effect of treatment on pain severity using PRO data throughout the trial, regardless of whether additional medications were used. Alternatively, the use of additional medications could be considered a signal of pain severity and incorporated into a composite estimand. Lastly, an estimand may also describe the effect on a subset of patients (eg, patients who would not take additional medications regardless of their assigned treatment).

Estimands for Real-World Data

Although trials are essential for comparing the effects of interventions, not all clinical questions can be answered using trial data. Moreover, trial eligibility criteria restrict some patients from participation. For example, the underrepresentation of older, sicker, and higher-risk patients in trials is a well-known issue.[3] Nonetheless, understanding the effect of treatments for those patients is of interest. Observational studies and RWD offer the opportunity to understand treatment effects over a longer time period and in a broader population, but they require assumptions that cannot be verified from the data. Additionally, RWD can be relevant in trial contexts as external control data for single-arm trials.

Claims data are a critical and frequently used data source for RWD. Unlike a trial, RWD is already available before the study inception. To ensure the objectivity of such studies, it is important to define the estimands prior to examining and analyzing the outcomes.[4] The definition of estimands in observational studies will be impacted by the structure of the databases. Not all relevant measurements or events may be included in claims data, or well-captured if they are included. This can make it difficult to define clinically relevant events and thus estimands. Consideration of the data structure and documentation of relevant events is critical for choosing estimands with RWD. For example, when using claims data, date of progression is often uncertain, and creating estimands for progression surrogates such as treatment duration can be challenging. In these situations, estimands might not be able to address this complexity, and additional sensitivity analyses would be required. Effect estimation that relies entirely on estimands should generally be limited to variables that can be supported by available data.

> Using estimands can help HEOR trialists and researchers measure and clearly communicate treatment effects.

Adjusting for rescue medication is one possible example of an estimand used in RWD. After defining which therapies might be considered as rescue medication, it is possible to create a composite endpoint that defines the progression of severe disease or death as the end of treatment medication or the introduction of a concurrent rescue therapy.

Planning Your Study

Systematic and careful consideration of the effects of intercurrent events on study endpoints is critical for choosing estimands. For registration trials, early communication with regulatory agencies is encouraged. This communication can ensure that the design and analysis plan are linked to the study objectives. Another important issue is sensitivity analysis. All statistical analyses rely on assumptions, and in all contexts (but especially in regulatory contexts) the sensitivity of study results to these assumptions is essential. Sensitivity analyses for estimands can assess the robustness of the treatment effect to different assumptions of the analytic methods. Trial and study planning should

include sensitivity analyses, and these can be included in the discussion with regulatory agencies.

Critically, early input from patients and clinicians can also help choose the right set of estimands for a study. Talking to patients and understanding which treatment effects would be meaningful for them is important. Clinician input is essential for ensuring that the estimands are relevant in the clinical context. In collaboration with statisticians, patients, and researchers with relevant expertise, early planning and consideration can result in clinically relevant, meaningful estimands.

The collaboration needed for choosing the proper estimands is also important for interpreting estimand results. Carefully designed and planned estimands can make study results easier to interpret. Using estimands can help HEOR trialists and researchers measure and clearly communicate treatment effects. In turn, patients, regulators, and payers can use estimands to make more informed decisions.

References

1. Food and Drug Administration, US Department of Health and Human Services. *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials: Guidance for Industry*. Silver Spring, MD. Accessed June 17, 2022. https://www.fda.gov/media/148473/download.

2. Bottomley A, Pe M, Sloan J, et al. Moving forward toward standardizing analysis of quality of life data in randomized cancer clinical trials. *Clin Trials*. 2018;15(6):624-630. doi:10.1177/1740774158795637

3. Jin S, Pazdur R, Sridhara R. Re-evaluating eligibility criteria for oncology clinical trials: analysis of investigational new drug applications in 2015. *J Clin Oncol*. 2017;35(33):3745-3752.

4. Rubin DB. For objective causal inference, design trumps analysis. *Ann Appl Stat*. 2008;2(3):808-840.

Building Cost-Effectiveness Thresholds for the Future

Dimitrios Kourouklis, PhD, Chris Sampson, PhD, Mikel Berdud, PhD, Chris Skedgel, PhD, Office of Health Economics, London, England, United Kingdom

A literature review reveals that many factors may independently or jointly influence the supply and demand for healthcare technologies and thereby influence an "optimal" cost-effectiveness threshold.

The application of a cost-effectiveness threshold in policy requires balancing with multiple objectives, which must be clearly understood to identify an optimal threshold.

Policy makers should clearly specify the scope and purpose of cost-effectiveness thresholds as distinct from other mechanisms in the decision-making process.

By broadening the scope of cost-effectiveness threshold estimation, considering various determinants of supply and demand, researchers may provide policy makers with a more complete picture to inform resource allocation.

A primer on thresholds

Novel health technologies are routinely both cost-increasing and health improving. Researchers and policy makers have used cost-effectiveness thresholds (CETs) to determine whether a technology's health benefits are worth the additional cost. Simply put, a CET represents the maximum price per quality-adjusted life year (QALY) at which policy makers would *usually* judge a technology to be a worthwhile investment. The use of CETs in policy varies across countries and healthcare systems. CETs may be specified explicitly (as in the case of England or of ICER in the United States) or implicitly (as in the case of Australia or Canada).[1]

> Researchers and policy makers have used cost-effectiveness thresholds (CETs) to determine whether a technology's health benefits are worth the additional cost.

Historically, 2 approaches to identifying a CET have been discussed.[2] One approach relies on the identification of society's willingness to pay (WTP) for a QALY (sometimes called a "demand-side" approach). The other relies on estimating the opportunity cost of current expenditure on healthcare, usually in recognition of a fixed budget (sometimes called a "supply side" approach). The opportunity cost approach has been the subject of numerous empirical analyses in recent years. It represents the intuitive notion that, without an excess budget to spend, we should only invest in a technology if we can disinvest in something less cost-effective, thereby increasing overall health gain.[3,4] Where a CET is not specified (explicitly) in policy, decisions may be informed by past allocation decisions or decisions in other countries.[5] This approach may indicate an implicit threshold but may undermine transparency and consistency in decision making.

More recently, research on CETs has moved toward the development of new theoretical frameworks, based on demand and supply models for healthcare technologies (confusingly, this is distinct from the demand-side and supply-side approaches mentioned earlier). These models seek to facilitate maximization of the total value created by investment in new technologies. This is known as the economic surplus (the sum of consumers' and producers' surplus) and the models focus on the distribution of this surplus between healthcare providers, patients, and the life sciences industry.[6] In the context of these models, numerous factors may influence the demand and supply of health technologies (including pharmaceuticals, medical devices, and nondrug interventions), such as the distribution of bargaining power and the nature and dynamics of research and development (R&D) costs.[7]

In this article, we consider these policy-focused research developments and review relevant literature to explore what factors might be used to determine CETs in future.

Connecting evidence to policy

One of the first studies to estimate a supply-side CET was conducted by Claxton et al (2015) in the context of the English National Health Service (NHS).[8] That study sought to identify the impact of expenditure on health outcomes and concluded that the current allocation of resources produced QALYs at the cost of around £12,936. This estimate was substantially lower than the threshold used by the National Institute for Health and Care Excellence (NICE) of £20,000-£30,000 per QALY. However, the central estimate was conditional on numerous assumptions—some of which faced criticism[9]—and different assumptions would lead to different estimates. In 2019, the Voluntary Scheme for Branded Medicines Pricing and Access, agreed

between the pharmaceutical industry and the government, maintained NICE's current threshold of £20,000-£30,000 per QALY.[10]

Similar studies have been conducted and similar policy-making tales can be told for Spain,[11] Australia,[12] and a growing number of other countries.[13] Most countries do not make use of explicit CETs in policy, and where CETs are used, they are not clearly based on evidence.[1] Researchers should consider why the empirical evidence generated to date has not been used to to inform policy.

The evidence generated from these studies examines the impact of current health expenditure on health outcomes, inferring the value of new technologies from the productivity of prevailing care. This is a notoriously difficult thing to estimate with confidence due to the two-way relationship between spending and outcomes, the limited availability of data, and a variety of other technical challenges. Furthermore, these opportunity cost estimates only provide part of the resource allocation puzzle. By broadening the scope of CET estimation (beyond estimates of productivity and informed by various determinants of supply and demand), researchers may be able to provide policy makers with a more complete picture. Currently, there is limited scope for evidence to inform policy on CETs. In the future, a more comprehensive approach may prove successful.

Taking stock of the possibilities

Expanding the scope of CET identification raises the inevitable question: what factors should be considered? Researchers—particularly economists—have recommended numerous factors when considering CETs and pricing policies. To date, nobody has conducted a thorough assessment of these factors.

We conducted a literature review to identify papers in which researchers have modeled—or otherwise proposed—the inclusion of different factors in the identification of a CET. Our objective was to generate a list of candidate factors for inclusion in a framework to identify a CET using models of demand and supply. We sought to classify these factors according to their characteristics in order to guide future research.

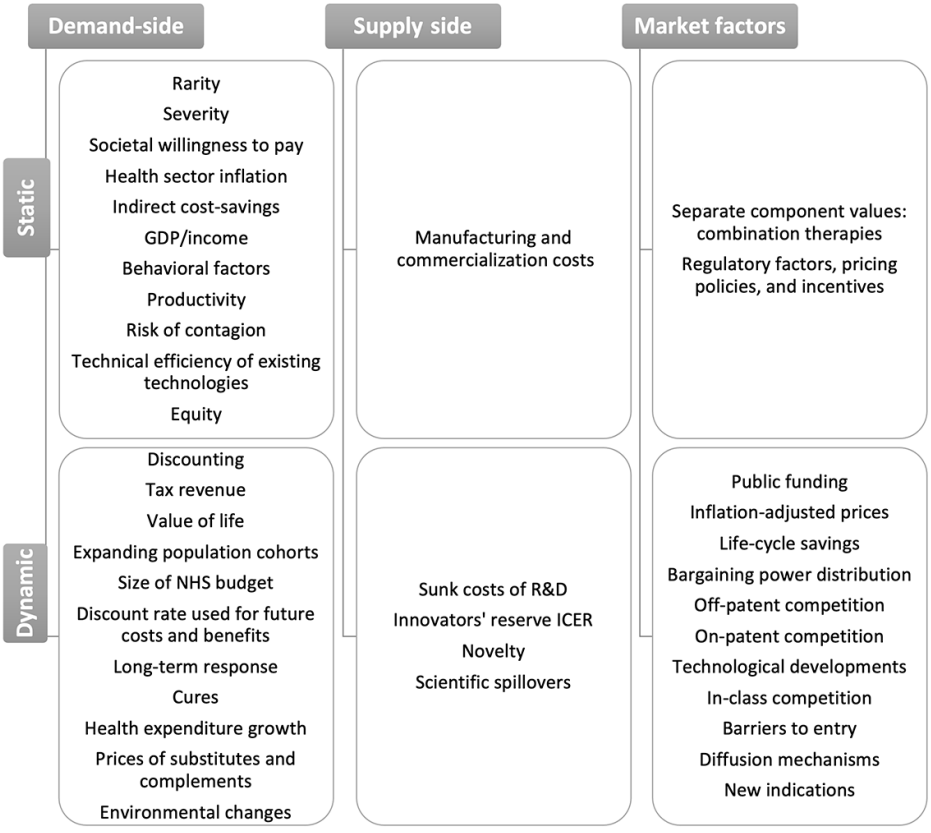
> It may be more productive for research to pursue some factors over others; some factors may have been extensively researched while others may simply be ideas recorded in print.

Our review identified 40 unique factors that have been discussed in the literature. We identified 22 demand-side, 5 supply-side, and 13 market factors—all summarized in **Figure 1**. The relationship between factors and the CET could also be classified as static when their whole impact can be consistently estimated at a point in time, or as dynamic when the size and/or sense of their impact show important dependencies over the life cycle of a product.

Demand-side factors are those that determine the level of demand for healthcare, including factors such as hyperbolic discount rates, budget mechanisms, tax revenue, and population growth. Supply-side factors determine decisions by manufacturers about whether to enter the market and their decisions about the level of R&D investment that determines future supply of new health technologies. These factors include the costs of R&D and innovators' reserve incremental cost-effectiveness ratios (ICERs)—the minimum ICER at which innovators will keep investing in R&D. Market factors may influence supply and demand and their interaction. These include factors such as inflation, competition, bargaining power distribution, and regulatory conditions.

It may be more productive for research to pursue some factors over others; some factors may have been extensively researched while others may simply be ideas recorded in print. We assessed

Figure 1. Identified factors



GDP indicates gross domestic product; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; R&D, research and development.

Table 1. Factor assessment criteria

Criterion/ Assessment	Good	Moderate	Poor
Quality of research	Mainly peer-reviewed papers in top field journals, journals with an impact factor of more than 1, highly cited and field expert authors	Mainly peer-reviewed papers with an impact factor of less than 1; academic working papers and reports	Mainly journalism, media news, blogs, etc
Quantity of research	Extensive literature including systematic reviews and perceived importance	Sufficient literature, few reviews available	Scarce literature with only a few papers available
Feasibility	Quantifiable and observable factor	Potentially quantifiable and observable factor, or only under specific circumstances	Factor cannot be quantified or observed
Relevance	Related to HTA processes and the UK context	Partially related to HTA processes and UK/other countries context	Factor unrelated to HTA process and country-specific context
Separability	Separable from quantifiable technology-specific inputs to HTA	Partially quantifiable for individual technologies or categories, or otherwise uncertain	Factor that varies across technologies and/or can be accounted for within evaluations or using modifiers

HTA indicates health technology assessment; UK, United Kingdom.

each factor according to its satisfaction of the criteria presented in **Table 1** and discussed our findings with an expert advisory group comprising academics and industry representatives.

Based on the subjective assessment and meetings with the expert advisory group, we prioritized and short-listed the following factors as those with greatest potential to play a practical role in the specification of a new framework to identify CETs:

1. Opportunity cost and displacement
2. Budget changes and flexibility
3. Nominal drug prices and inflation
4. Market regulation and competition
5. Bargaining power distribution
6. Elasticity of response of innovators

A substantial body of literature is available for each of these factors and future work should explore the feasibility of incorporating each of these into the identification of a threshold. For instance, it may be possible to establish—in theory and evidence—the extent to which a higher budget (all else equal) corresponds to a higher CET.[14]

A complex picture

Our literature review uncovered some challenges relating to the appropriate definition of CETs, assumptions underlying each factor, and data availability. In particular, researchers often conflate price and value by regarding CETs as an implicit price-setting mechanism (ie, the notion of manufacturers "pricing to the threshold"). We believe it is important to disentangle these elements: the ICER should be interpreted as the price per unit of effect, while thresholds should be used to guide decision makers on the acceptability of that price, in conjunction with other criteria and value judgments.

More broadly, it is essential to distinguish the different mechanisms for decision making and the various inputs to technology assessment and reimbursement processes. Each of the factors that has been proposed to determine CETs or optimal prices may be most appropriately accounted for via one of several mechanisms. Some of the key mechanisms that are relevant to the factors that we have identified are (i) inclusion within an economic evaluation, (ii) adoption as a quantitative modifier, and (iii) qualitative consideration within an appraisal.

Health economic evaluations should account for all factors that affect the costs and outcomes associated with a specific technology. These will influence the technologies, ICER (which can then be judged against a CET). Modifiers indicate differences in the value of outcomes across different groups of technologies. They are generally used to address equity concerns and should be used to weight QALYs (rather than to identify product- or condition-specific thresholds per se). The appraisal process should incorporate the available quantitative, qualitative, and deliberative input to the decision and is an important mechanism for considering those factors that cannot be easily represented in evidence.

Once the most appropriate factors to consider in the estimation of a CET have been identified, and factors more appropriately considered as part of the ICER have been excluded, data availability and gaps in the research pose further challenges. Researchers must consider what is feasible in different settings.

The way forward

Research on cost-effectiveness thresholds has developed substantially in recent years and there are signs that it is shifting in a new direction. Researchers are right to look beyond the relationship between expenditure and outcomes in healthcare to understand CETs. Our research highlights a vast number of factors that could—in principle—be considered in the identification of a CET.

The adoption of evidence-based policy in defining CETs—whether in terms of opportunity cost or societal willingness to pay—is a worthy objective that could ultimately benefit the health of the population by facilitating a more efficient, health-maximising allocation of resources in healthcare. However, the factors that we have identified paint a complex picture. A cost-effectiveness threshold cannot be

adopted as a catch-all value assessment tool. Many factors that determine optimal prices and the relative value of technologies should be incorporated via mechanisms other than a CET.

In navigating this complex landscape, the duty falls as much to policy makers as to researchers. Policy makers should clearly specify the scope and purpose of CETs, as distinct from other mechanisms in the decision-making process. Researchers should explore data sources and develop new methods to incorporate appropriate factors in identifying a CET. It is for the common good to develop a robust framework for the determination of CETs that can support resource allocation while accounting for all relevant factors that may influence current and future population health. It is imperative for researchers and policy makers to adopt a holistic view in the identification and use of cost-effectiveness thresholds and, more broadly, the allocation of healthcare resources. New frameworks and approaches should be considered in countries where explicit thresholds are specified, as well as contexts with less formalized resource allocation processes.

Funding/Support:
This work was funded by the Association of the British Pharmaceutical Industry (ABPI). The views presented do not represent those of the ABPI.

References

1. Zhang K, Garau M. *International Cost-Effectiveness Thresholds and Modifiers for HTA Decision Making*.; 2020. Accessed February 4, 2022. https://www.ohe.org/publications/international-cost-effectiveness-thresholds-and-modifiers-hta-decision-making.

2. Vallejo-Torres L, García-Lorenzo B, Castilla I, et al. On the estimation of the cost-effectiveness threshold: why, what, how? *Value Health*. 2016;19(5):558-566. doi:10.1016/j.jval.2016.02.020

3. Pekarsky BA. The "New Drug Reimbursement" Game. In: *The New Drug Reimbursement Game*. Springer; 2015:127-162.

4. Thokala P, Ochalek J, Leech AA, Tong T. Cost-effectiveness thresholds: the past, the present and the future. *PharmacoEconomics*. 2018;36(5):509-522. doi:10.1007/s40273-017-0606-1

5. Eichler HG, Kong SX, Gerth WC, Mavros P, Jönsson B. Use of cost-effectiveness analysis in health-care resource allocation decision-making: how are cost-effectiveness thresholds expected to emerge? *Value Health*. 2004;7(5):518-528. doi:10.1111/j.1524-4733.2004.75003.x

6. Patented Medicine Prices Review Board. *Working Group to Inform the PMPRB Steering Committee on Modernization of Price Review Process Guidelines - Final Report*. 2019. Accessed February 2, 2022. http://pmprb-cepmb.gc.ca

7. Berdud M, Ferraro J, Towse A. *A Bargaining Approach: A Theory on ICER Pricing and Optimal Level of Cost-Effectiveness Threshold*. Office of Health Economics; 2020. Accessed July 5, 2021. https://www.ohe.org/publications/bargaining-approach-theory-icer-pricing-and-optimal-level-cost-effectiveness-threshold

8. Claxton K, Martin S, Soares M, et al. Methods for the estimation of the National Institute for Health and Care Excellence cost-effectiveness threshold. *Health Technol Assess*. 2015;19(14):1-503, v-vi. doi:20150217140715559

9. Barnsley P, Towse A, Karlsberg Schaffer S, Sussex J. *Critique of CHE Research Paper 81: Methods for the Estimation of the NICE Cost Effectiveness Threshold*. 2013. Accessed July 5, 2021. https://www.ohe.org/publications/critique-che-research-paper-81-methods-estimation-nice-cost-effectiveness-threshold

10. DHSC. *The 2019 Voluntary Scheme for Branded Medicines Pricing and Access*. 2018. Accessed June 28, 2022. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/761834/voluntary-scheme-for-branded-medicines-pricing-and-access-chapters-and-glossary.pdf

11. Vallejo-Torres L, García-Lorenzo B, Serrano-Aguilar P. Estimating a cost-effectiveness threshold for the Spanish NHS. *Health Econ*. 2018;27(4):746-761. doi:10.1002/hec.3633

12. Edney LC, Haji Ali Afzali H, Cheng TC, Karnon J. Estimating the reference incremental cost-effectiveness ratio for the Australian health system. *Pharmacoeconomics*. 2018;36(2):239-252. doi:10.1007/s40273-017-0585-2

13. Edney LC, Lomas J, Karnon J, et al. Empirical estimates of the marginal cost of health produced by a healthcare system: methodological considerations from country-level estimates. *PharmacoEconomics*. 2022;40(1):31-43. doi:10.1007/s40273-021-01087-6

14. Brouwer W, van Baal P, van Exel J, Versteegh M. When is it too expensive? Cost-effectiveness thresholds and health care decision-making. *Eur J Health Econ*. 2019;20(2):175-180. doi:10.1007/s10198-018-1000-4

Benefit-Sharing Programs: What Role May They Play in Supporting Cost-Effective Prescribing Practices for High-Cost Biologics?

Teresa Barcina Lacosta, MSc, PharmD, KU Leuven, Leuven, Belgium; **Arnold G. Vulto, PharmD, PhD**, Erasmus University Medical Center, Rotterdam, The Netherlands; **Adina Turcu-Stiolica, PhD**, University of Medicine and Pharmacy of Craiova, Craiova, Romania; **Isabelle Huys, PhD**, KU Leuven, Leuven, Belgium; **Steven Simoens, MSc, PhD**, KU Leuven, Leuven, Belgium

Benefit-sharing strategies are not a panacea but can support the rational and cost-effective prescribing of biologics.

Savings achieved via benefit sharing can be successfully reinvested to improve patient care.

Benefit-sharing programs deserve careful planning and monitored execution to avoid stakeholder demotivation and implementation failures.

The main obstacle to optimal benefit-sharing implementation appears to be the lack of transparency regarding the distribution/reinvestment of savings. This has raised questions on how to optimally engage all stakeholders involved in decision making.

Making medicines more accessible: the role of generic and biosimilar medicines

Recent analyses on the evolution of the global medicines market show a growing trend in medicine use and spending across all disease areas. Especially in oncology and in the field of immune-mediated inflammatory diseases, the increased use of high-cost biologics has become an important driver of pharmaceutical spending.[1] According to the Organization for Economic Co-operation and Development (OECD), multiple countries have raised concerns about their ability to reconcile access with spending efficiency and sustainability.[2]

> According to the OECD, multiple countries have raised concerns about their ability to reconcile access with spending efficiency and sustainability.

The urgency to address these concerns is even higher in low- and middle-income countries, where significant access delays occur throughout the care continuum.[3] In this context, the market entry of more affordable non-innovator generic and biosimilar medicines represents an opportunity to induce price competition, increase spending efficiency, and expand access to medications while maintaining the quality-of-care standards. The World Health Organization (WHO) pre-qualification and listing of generics and biosimilars has supported the use of these medicines worldwide.[4] According to WHO data, the introduction of antiretroviral generic medicines allowed scaled-up access to these therapies globally.[5] Likewise, the recent WHO listing of biosimilars for essential medicines such as trastuzumab is expected to increase global patients' access to cancer care.[4,6] Despite the role that generic and biosimilar medicines play in supporting patients' access to treatments, multiple factors determine prescribing choices and the selection of "best-value" pharmaceuticals (generally generics and biosimilars) is not always prioritized. In this commentary, we examine the role that benefit-sharing strategies may play in supporting cost-effective prescribing practices for biologics across Europe.

Benefit-sharing initiatives can promote the cost-effective prescribing of biologics

Barriers have existed and still exist to the acceptance and use of biosimilars. Prescribers and patients have historically raised concerns about the safety and efficacy of these medicines, especially around the safety of switching and substituting biosimilars with the originator product or with other biosimilars. Although uncertainties surrounding these aspects have been addressed after more than 10 years of biosimilars market availability in Europe,[7,8] prescribers and patients still highly value the possibility to choose between originator and biosimilar products.[9]

To control spending in pharmaceuticals, diverse policies have been implemented to support the use of best-value biologics (prescription quotas, benefit-sharing initiatives, etc), and to disincentivize prescribing less affordable biologics (reimbursement restrictions and budget caps). Experience tells us that policies limiting the reimbursement of pharmaceuticals, as well as policies applying prescription quotas, are perceived negatively by certain stakeholders. Across Europe, these policies have been generally applied in combination with (1) educational campaigns on biosimilars, and (2) benefit-sharing (gainsharing) initiatives aimed at generating consensus on the importance of promoting cost-effective prescribing practices for biologics. The combination of these strategies can increase the willingness of healthcare professionals (HCPs) and patients to use biosimilars, especially if it is communicated that this would lead to higher access to

treatments, reduced healthcare costs, and general societal benefits.[9]

Although there are multiple examples in the literature of educational initiatives for biosimilars, little is known about where and how to implement benefit-sharing programs. Benefit-sharing programs can be defined as incentive programs that promote the use of best-value biologics by motivating changes in prescribing practices. The aim of these programs is to generate savings that can be shared among the stakeholders involved (eg, health authorities/payers/insurers, hospital financial departments, healthcare professionals) and that can be reinvested to fund innovation, increase patients' access to treatments, and make quality of care improvements.

Our recent study in *BioDrugs* provides a detailed inventory of benefit-sharing cases.[10] Based on these cases, it has been possible to (1) identify challenges that institutions face when implementing benefit-sharing programs and (2) formulate best-practice recommendations for benefit sharing. With the current commentary, we aim to increase policy makers' awareness of these aspects. Our main goal is to support informed decision making for institutions that may implement benefit-sharing programs in the future.

The promise of implementing benefit-sharing programs: implications for key stakeholders

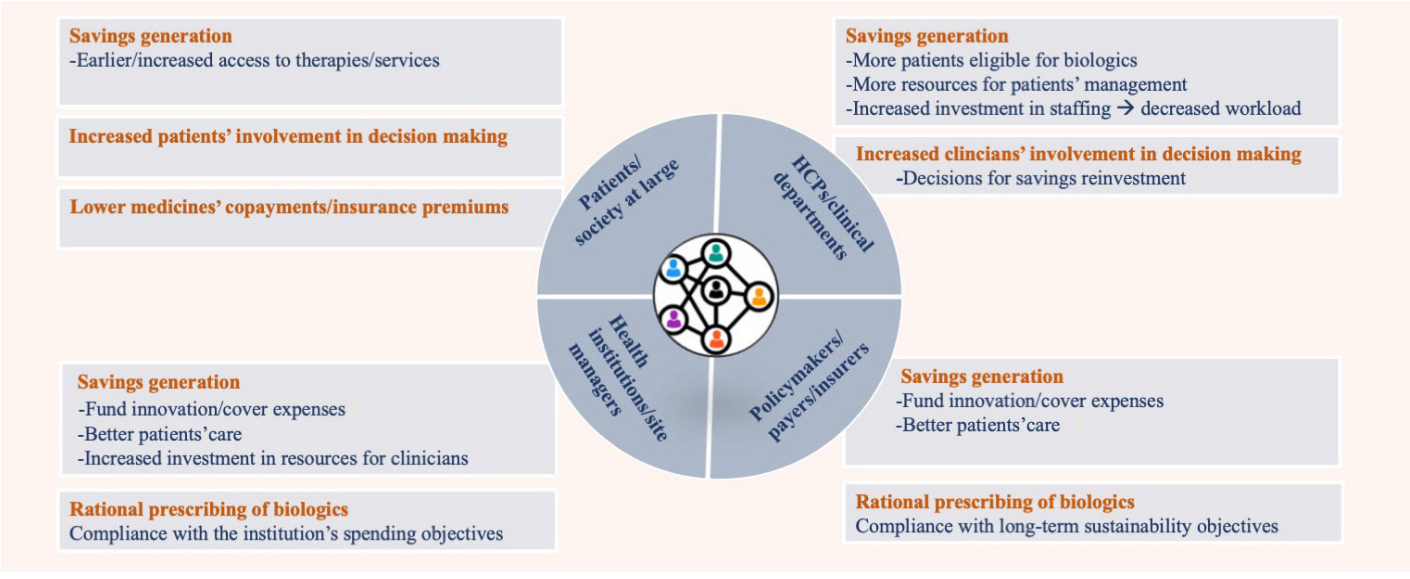
To date, multiple countries across Europe have launched benefit-sharing initiatives for biologics (ie, the United Kingdom, France, Germany, Ireland, Italy, The Netherlands, Portugal, and Sweden). These examples showed us a set of characteristics that are generally pursued by organizers of benefit-sharing programs. Most benefit-sharing programs implemented in Europe have aimed to:

- Set prescription objectives for best-value biologics
- Evaluate prescribers' compliance with the set prescription objectives
- Generate savings and reinvest them according to the needs of the stakeholders who produced them
- Establish pathways for savings reinvestment that enable funding health services and quality of care improvements

This general scope of benefit-sharing initiatives can be illustrated, for example, by the Irish National benefit-sharing program.[11] In Ireland, the benefit-sharing initiative was focused on the TNF-α inhibitor products adalimumab and etanercept. The first step in the implementation of this initiative was to establish criteria for the identification of best-value biologics. The application of these criteria led to the selection of various adalimumab and etanercept biosimilars as best-value products. For these products, an 80% prescription objective was set to be achieved in a defined timeframe. The hospital clinical departments that initiated or switched eligible patients to best-value biologics received €500 of the resulting savings per patient. One year after the implementation of the Irish benefit-sharing initiative, the uptake of best-value products had considerably increased and savings amounted to €22.7M. Approximately 16% of the generated savings were returned to the hospital clinical departments for reinvestment into improvements in the provision of care (eg, increased infusion room's capacity for intravenous formulations, development of electronic patient registries).

The Irish benefit-sharing initiative represents just one example of the benefits to be achieved via benefit sharing. In **Figure 1** we provide a more comprehensive list of potential benefits that can be realized for the different stakeholder groups involved. However, the examination of benefit-sharing cases across Europe suggests that

Figure 1. Outline of benefits that can potentially be realized via the implementation of benefit-sharing programs for best-value biologics. For each stakeholder group, we provide a list of the most relevant benefits to be achieved.



HCP indicates healthcare provider.

the promise of implementing benefit-sharing programs (**Figure 1**) has only been partially delivered. In some cases, patients were not informed about the outcomes achieved via benefit sharing and about how their participation in these programs improved their care. Furthermore, HCPs and clinical departments were not always able to participate in decisions regarding the reinvestment of savings. This has been partly due to time constraints that hindered the preparation of formal reinvestment plans and to the urgency to reallocate savings to cover expenses in other care areas. These aspects evidence a general lack of transparency regarding financial flows. Also, the evaluation of the success of implemented benefit-sharing programs was opaque in some instances. Therefore, it has been uncertain how to determine the direct impact of benefit-sharing programs on patients' care. We include in **Table 1** a summary of challenges faced by institutions when implementing benefit-sharing programs. The relative relevance of these challenges for each implementation setting has primarily depended on factors like the degree of centralization of the healthcare system; the available communication channels between managers, HCPs, and patients; the policy environment; and the specific implementation timeframe.

> Despite the role that generic and biosimilar medicines play in supporting patients' access to treatments, multiple factors determine prescribing choices and the selection of best-value pharmaceuticals (generally generics and biosimilars) is not always prioritized.

The challenges associated with the implementation of benefit-sharing programs have raised questions about how to actively engage all the stakeholder groups in decision making, and how to fully deliver on the promise of benefit sharing in the future.

Strategies moving forward to optimize the implementation of benefit-sharing initiatives

Our research conducted on benefit-sharing cases in Europe shows that there is no one-size-fits-all best approach for the successful design and implementation of benefit-sharing programs. As discussed before, the conditions for benefit sharing need to adapt to the specific socioeconomic background of the country, the characteristics of the healthcare system, the clinical context, and the regulatory and political environment. A point of practical consideration is that if the use of best-value biologics is already optimal or if the savings potential associated with the use of best-value pharmaceuticals is low, it may not be economically advantageous for the payer to apply benefit-sharing strategies. Also, in countries where the spending on biologics is low, the application of benefit-sharing initiatives may not be relevant. These aspects are to be considered carefully by future benefit-sharing implementers.

> The challenges associated with the implementation of benefit-sharing programs have raised questions about how to actively engage all the stakeholder groups in decision making.

While acknowledging the importance of considering the particularities of each implementation setting, it is possible to formulate some general best practice recommendations. To realize the full potential of benefit-sharing programs, greater attention should be paid to the following 5 aspects: (1) informing HCPs and institutions of the principles of benefit sharing in advance; (2) setting up and monitoring success indicators for benefit-sharing programs on a timely basis; (3) including quality of care parameters as success indicators; (4) establishing clear pathways for the transparent distribution and reinvestment of savings; and (5) transparently communicating with patients about the outcomes of benefit-sharing programs.

These key recommendations, extracted from the observation of benefit-sharing cases in Europe, could be applicable to other jurisdictions. However, institutions implementing benefit-sharing initiatives in the future should determine first whether the socioeconomic/ regulatory environment of their countries and the healthcare system organization would make this implementation feasible and advantageous. We hope that the learnings outlined in this commentary can serve as a starting point to guide future implementers of benefit-sharing programs.

Table 1. Overview of most relevant challenges faced by institutions when implementing benefit-sharing programs for biologics.

Overview of design/implementation challenges
Lack of guidance on how to design/implement benefit-sharing programs
Lack of transparency/publicly available data on the outcomes of benefit-sharing programs
Insufficient resources for the timely monitoring of benefit-sharing outcomes
Lack of appropriate indicators to monitor improvements in patients' outcomes and care
Insufficient time: • Affects healthcare professionals' capacity to inform patients about benefit sharing • Affects managers' capacity to present a robust business case for benefit sharing and to plan the reinvestment of savings in advance
Reduction over time of the savings potential achievable via benefit sharing
Changes in the **regulatory environment**
Communication barriers and unreceptiveness of stakeholders

References

1. IQVIA Institute for Human Data Science. Global Medicines Spending and Usage Trends, Outlook to 2025. 2021. Accessed June 16, 2022. https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/global-medicine-spending-and-usage-trends-outlook-for-2025/iqvia-institute-global-medicines-and-usage-trends-to-2025-0421-forweb.pdf

2. OECD. Better Policies for Better Lives. Addressing Challenges in Access to Oncology Medicines. Analytical Report. 2020. Accessed June 17, 2022. https://www.oecd.org/health/health-systems/Addressing-Challenges-in-Access-to-Oncology-Medicines-Analytical-Report.pdf

3. Brand NR, Qu LG, Chao A, Ilbawi AM. Delays and barriers to cancer care in low- and middle-income countries: a systematic review. *Oncologist*. 2019;24(12):e1371-e80. doi:10.1634/theoncologist.2019-0057

4. World Health Organization (WHO). World Health Organization Model List of Essential Medicines. 22nd List. 2021. Accessed June 17, 2022. https://apps.who.int/iris/bitstream/handle/10665/345533/WHO-MHP-HPS-EML-2021.02-eng.pdf

5. World Health Organization (WHO). Generic medicines. Interchangeability of WHO-prequalified generics. WHO Drug Information. 2016;30(3). Accessed July 18, 2022. https://apps.who.int/iris/handle/10665/331014

6. McBride A, Balu S, Campbell K, Bikkina M, MacDonald K, Abraham I. Expanded access to cancer treatments from conversion to neutropenia prophylaxis with biosimilar filgrastim-sndz. *Future Oncol*. 2017;13(25):2285-95. doi:10.2217/fon-2017-0374

7. Barbier L, Vulto AG. Interchangeability of biosimilars: overcoming the final hurdles. *Drugs*. 2021;81(16):1897-903. doi:10.1007/s40265-021-01629-4

8. Kurki P, Barry S, Bourges I, Tsantili P, Wolff-Holz E. Safety, immunogenicity and interchangeability of biosimilar monoclonal antibodies and fusion proteins: a regulatory perspective. *Drugs*. 2021;81(16):1881-96. doi:10.1007/s40265-021-01601-2

9. Barbier L, Simoens S, Vulto AG, Huys I. European stakeholder learnings regarding biosimilars: part i-improving biosimilar understanding and adoption. *BioDrugs*. 2020;34(6):783-96. doi:10.1007/s40259-020-00452-9

10. Barcina Lacosta T, Vulto AG, Turcu-Stiolica A, Huys I, Simoens S. Qualitative analysis of the design and implementation of benefit-sharing programs for biologics across Europe. *BioDrugs*. 2022. doi:10.1007/s40259-022-00523-z

11. Duggan B, Smith A, Barry M. Uptake of biosimilars for TNF-α inhibitors adalimumab and etanercept following the best-value biological medicine initiative in Ireland. *Int J Clin Pharm*. 2021. doi:10.1007/s11096-021-01243-0

Health Equity for HTA

A Conversation With Wanrudee Isaranuwatchai, PhD

Section Editor: **Marisa Santos, PhD, MD,** Instituto Nacional de Cardiologia, Rio de Janeiro, Brazil

Photo courtesy of Wanrudee Isaranuwatchai

Q&A

"Real-world evidence has been the talk of the town for some time. It would be informative to see how real-world data could be used to support this appetite of data from methods such as DCEA and ECEA."

Recently, I had the pleasure of interviewing Wanrudee Isaranuwatchai, PhD, Program Leader and Senior Researcher of the Health Intervention and Technology Assessment Program (HITAP) in Thailand. She is also an Affiliated Scientist at St. Michael's Hospital and an Associate Professor at the Institute of Health Policy, Management, and Evaluation at the University of Toronto in Canada.

Dr Isaranuwatchai's research focuses on how to apply health economics and health technology assessment (HTA) in the real-world setting as well as how to advance methods in economic evaluation. Her experience and keen interest in the potential use of big data in health economics and HTA to support evidence generation and the policy-making process make her an ideal person to share her perspective on this month's theme of improving equity through HTA.

VOS: In recent years, the subject of health equity has gained popularity in HTA. What is causing so much interest in your point of view?

Wanrudee Isaranuwatchai: In the words of Nelson Mandela, "Health cannot be a question of income; it is a fundamental human right." Health equity has always been an important topic in our society including in the field of HTA. Evolution of incorporating equity was reflected in the updated definitions of HTA.[1] One could consider inequity as a long-standing challenge in our HTA field to have an approach that enables the consideration of health equity into economic evidence. Public health is about ensuring that no one is left behind while overall health improves.[2] This goal is achieved through equitable access in healthcare, which is also a key feature of global health policy agendas and the universal health coverage movement. Therefore, many would consider equity to be one of the essential parts of public health policy.

Although recognizing that health inequity is a concern is a good first step, the COVID-19 pandemic brought forward the reality that talking about it will not address it.[3] Many are recognizing that the long-standing socioeconomic inequities disproportionately affecting vulnerable and marginalized populations are now wider than ever, especially when there are public health emergencies. In our work to help identify best buys, wasted buys, and contestable buys for noncommunicable disease (NCD) prevention,[4,5] the results identify several considerations to use when deciding whether and how to implement an NCD prevention intervention—and health equity was one of those considerations.

VOS: To what extent do HTA reports include pertinent information about equity issues? Do they actually alter how decisions are made in practice?

WI: There are movements to incorporate equity considerations as a part of HTA to support the policy- and decision-making process. Our team conducted a landscape analysis of HTA capacity in the Association of South-East Asian Nations region and identified that equity was a factor in the decision-making process for a few countries.[6]

Specifically in Thailand, several pieces of evidence are used to assist the policy makers before decisions are made on reimbursement for Universal Health Care Benefit Package and National List of Essential Medicines. Topic prioritization criteria include: (i) number of people affected by the disease or health problem; (ii) severity of the disease or health problem; (iii) effectiveness of the health technology; (iv) variation in practice; (v) impact on household expenditure; and (vi) equity, social, and ethical considerations. Meanwhile, decision-making criteria include: (i) cost-effectiveness; (ii) availability of clinical practice guidelines; (iii) health system readiness; (iv) budget impact; and (v) ethical and social issues. In both processes, the last component takes into consideration health equity before any decisions so that equity issues can influence how decisions are made in practice (as they should). Policy makers have also shown their interests and support to incorporate health inequity into the decision-making process, if possible, in a systematic and evidence-informed way. Engagement with stakeholders during the research process—including civil society in the board of the decision-making body—helps keep equity issues in sight. With that being said, the incorporation of health equity issues into economic evidence remains to be implemented.

In an ideal world, it would be easy and straightforward to prioritize and allocate resources to interventions that have the maximum impact on health, while ensuring fair and equitable distribution of resources to all and minimizing the risk of financial hardship from out-of-pocket payments. In the real world, however, things may be quite different. In our work on NCD prevention,[4,5] we recognized that, clearly, what is best or wasted is more than just a question of effectiveness and cost. There are other ethical, cultural, political, and practical factors that are crucial and should be considered when making decisions.

VOS: How could cost-effectiveness analysis (CEA) research on the consequences for health equity be more impactful?

WI: It is one thing to know that it is important but another to do something about it. The first step perhaps would be to recognize when the topic we are doing a CEA on has an equity consideration that should be taken into account. Subsequently, the traditional CEAs should then be adapted to explicitly incorporate health equity considerations using one of the existing methods (eg, a distributional cost-effectiveness analysis [DCEA], an extended cost-effectiveness analysis [ECEA]) so that the findings will be comprehensive and useful to policy makers.

Reporting standards, such as Consolidated Health Economic Evaluation Reporting Standards (CHEERS), have recently updated thier guidelines to include criteria on health equity, highlighting the importance of health equity and how it should be incorporated (when relevant) to CEA research.[7]

VOS: What are the central concepts of health equity that cost-effectiveness research can access?

WI: The overall goal of DCEA (which incorporates health equity) aligns with CEA in that these methods aim to provide evidence to support the decision-making process, but not to make the decisions for policy makers. Traditional CEA tells us whether an intervention provides a good value-for-money (referring to the efficiency aspect). This exploration is done by examining the trade-offs between health effects and costs associated with the interventions. What it does not show is how these health outcomes and costs are distributed across different population groups of interest. DCEA and ECEA are specifically designed to: (i) identify these population groups (which can vary by the topics, diseases, or intervention being assessed); and (ii) distribute the costs and health effects by such groups. Therefore, DCEA and ECEA can tell us both whether an intervention is a good value-for-money and whether the intervention enhances or reduces health equity. As a result, we can see the trade-offs between the impact on efficiency and equity from an intervention. This approach is useful as it helps us choose interventions depending on the objective of improving total health versus improving equity. These objectives are generally set by policy makers, but they should reflect the overall preference and need of the society at a given time.

Information from such analyses can be used to support several types of decisions such as designing benefit healthcare packages, purchasing certain health interventions, investing in healthcare infrastructure, or supporting public health initiatives that enhance both equity and efficiency.[8]

VOS: How can health initiatives affect socially disadvantaged groups and vulnerable people differently? Can you give some real-world examples?

WI: Socially disadvantaged groups and vulnerable people face additional challenges more than others. Seeking only to maximize health benefits can conflict with equity.[9] For example, achieving equity tends to become costlier as policy reaches out to less accessible, marginalized groups. At the same time, exclusion of hard-to-reach populations (including socially disadvantaged groups and vulnerable people) raises important ethical questions regarding a just distribution of access to healthcare and of health itself.

For example, DCEA has been used to assess the inequality impact of technologies recommended by National Institute of Health and Care Excellence in the United Kingdom between 2012 to 2014.[10] Among the 27 interventions that were evaluated, 14 interventions were estimated to increase population health and reduce health inequality, 8 to reduce population health and increase health inequality, and 5 to increase health and increase health inequality. A DCEA in Ethiopia explored the equity impact of a hypothetical redesigned rotavirus vaccination program.[11] The study found that diverting additional resources into vaccine delivery in rural areas resulted in not cost-effective but equity-enhancing outcomes and found the equity-efficiency trade-offs to be worthwhile given decision makers' objective to reduce health inequity. Another study utilized ECEA to explore the consequences of tobacco tax on household health and finances among rich and poor smokers in China over a 50-year period.[12] They found that such excise tax increase could be pro-poor in China as the years of life-year gained would

be more concentrated on the poor (79 million in the poorest quintile group) than on the rich (11 million in the richest quintile group), and the financial risk-protection benefits would be largely concentrated among the poorest quintile group (accruing about 70% of the total $2 billion of insurance value gained).

In one of our works on NCDs,[5] we found that every single day NCDs cause more than 100,000 deaths—80% of which occur in low- and middle-income countries.[13] Additionally, mental health problems are the leading cause of disability around the world. For example, approximately 800,000 people commit suicide every year and about 75% of those occur in low- and middle-income countries (LMICs).[14]

We see and experience discrepancies in health in all levels, and the question remains, what are we going to do about it if we are to be at this crossroad of efficiency and equity? Another example (a common phenomenon globally) could be the considerations to publicly fund high-cost drugs that mostly are not cost-effective but could reduce inequity. Having evidence on the equity-efficiency trade-offs has potential to assist real-world decisions.

VOS: What exactly does "extended cost-effectiveness analysis" entail?

WI: ECEA is another approach to address health policy assessment by capturing equity within decision making. The distinguishing feature of ECEA from traditional CEA and DCEA is its emphasis on financial risk protection.[15] ECEA helps analyze the distribution of both health benefits and financial risk protection benefits (prevention of illness-related impoverishment) per dollar expenditure for a specific policy, so this method is appropriate when policy makers are interested in examining the financial risk protection benefits of policies (where out-of-pocket payments may be high) and preventing medical impoverishment.

VOS: How might the net health benefits concept help to analyze the impact on equity?

WI: Net health benefit is another summary measure in HTA that aims to present the benefit in terms of health (rather monetary value) from the difference between the expected benefits of a decision and the expected associated opportunity costs.[8] DCEA applies the concept of net health benefit at the equity-relevant variable level (ie, population groups of interest) rather than at the general population level (which assumes equal effect) to incorporate equity into analysis by analyzing the distribution of benefits and opportunity costs. The forgone health benefits that could have been generated through the next-best alternative may be unequally distributed, and this distribution is required to estimate the net distributional health impact of a program. Three key pieces of information will be needed for this analysis: (i) the baseline distribution of health; (ii) distribution of health opportunity costs; and (iii) distribution of health benefits. However, the use of net health benefit alone (metric for efficiency) is not enough to comprehend and measure the impact on equity.

VOS: What is the concept behind the equity trade-off?

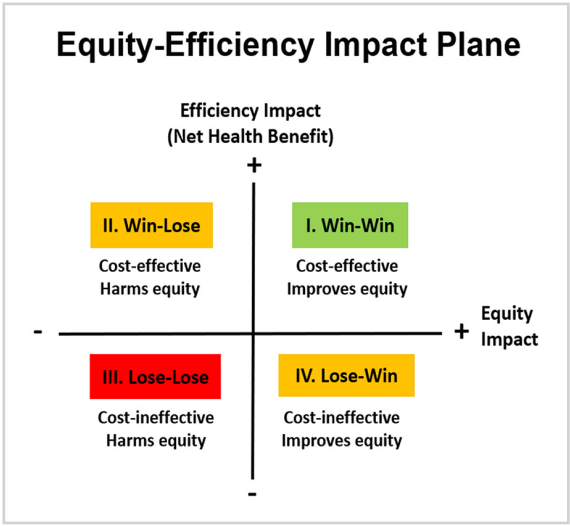
WI: HTA has often been criticized for its overemphasis on efficiency gains and lack of equity considerations in explicit forms. Traditional economic evaluations focus on the costs and effects of each intervention in an aggregated format. Impact of policies on equity can be measured using the DCEA approach by using metric that are of interest to policy makers. Reduction in an index of inequality in deprivation-related inequality in health-adjusted life expectancy has been used by researchers in England and Ethiopia to measure equity impact.

DCEA then utilizes combined information from net health benefit and equity impact to illustrate the underlying trade-offs between equity and efficiency as depicted by the equity-efficiency impact plane in **Figure** below. Interventions above the horizontal line are considered efficiency enhancing while those to the right of the vertical line are equity enhancing. This trade-off allows decision makers to keep their objectives in sight and in balance. In LMICs, vaccination and infectious disease control programs often fall into the northeast quadrant (enhancing both equity and efficiency), as they deliver large health gains per unit cost and disproportionately benefit socially disadvantaged groups. By contrast, investments in high-cost end-of-life treatments may fall into the southwest quadrant (reducing efficiency and widening equity gap) of being neither cost-effective nor likely to reduce social inequality in health. Hence, coverage of interventions in this quadrant will rely on other ethical and political arguments of value. In the northwest quadrant, the intervention is good for total health but bad for equity, and in the southeast quadrant, the option is bad for total health but good for equity. This can happen, for example, when socially disadvantaged groups gain less than advantaged groups from a decision to fund a medical technology, due perhaps to barriers to access, adherence, and long-term recovery, and additional investment in delivery infrastructure and follow-up care would be needed to facilitate equal access, adherence, and long-term recovery.

VOS: What priority research is required at the intersection of equity and HTA?

WI: There are now methods (eg, ECEA, DCEA) available to incorporate equity into economic evaluations (a part of HTA). Perhaps the priority now is to apply these methods to the real-world case studies (at least that is what we are trying to do in Thailand in collaboration with partners in United Kingdom and Singapore). A case study to show how innovative methods

Figure.



Source: Cookson, et al.[8]

such as DCEA can assist in the decision-making process in the real world can illustrate the future of improved decision-making processes that explicitly and systematically consider health equity. This first case study of DCEA in Thailand will illustrate how equity considerations can be formally analyzed and incorporated into decision making. This study can equip decision makers with the tools to improve health equity as well as comprehend the implications of prioritizing health programs solely based on efficiency gains. More importantly, this type of analysis can provide policy makers with information on how to design and implement an equity enhancing health intervention.

VOS: What are the primary obstacles to implementing these ideas?

WI: DCEA is a data-hungry method and it may not be possible to collect all relevant socioeconomic parameters (relevant to equity issues) in a study. We may only determine a few dimensions to incorporate equity considerations in CEA, which is largely dependent on the level of data that may be available. To mitigate this challenge, research teams should explore data from local contexts whenever possible, including the options of exploring expert elicitation and consulting international literature to obtain data for model parameters.

Furthermore, real-world evidence has been the talk of the town for some time. It would be informative to see how real-world data (RWD) could be used to support this appetite of data from methods such as DCEA and ECEA. Our network in Asia recognizes the potential of RWD and came together to create a nonbinding document to support the use of RWD.[16] However, for RWD to truly fulfill its potential to help address important issues such as health equity, different stakeholders (including governments, private sector, academics, and the public) must find harmony and balance in sharing big data while protecting data privacy.

References

1. O'Rourke B, Oortwijn W, Schuller T. The new definition of health technology assessment: a milestone in international collaboration. *Int J Technol Assess Health Care*. 2020;36(3);187-190.

2. Galea S. Race, history, and the science of health inequities. Boston University School of Public Health website. Published 2019. Accessed July 27, 2022. https://www.bu.edu/sph/news/articles/2019/race-history-and-the-science-of-health-inequities

3. Ten billion COVID vaccinations: world hits new milestone. *Nature* website. Published January 31, 2022. Accessed July 27, 2022. https://www.nature.com/articles/d41586-022-00285-2

4. Isaranuwatchai W, Teerawattananon Y, Archer RA, et al. Prevention of non-communicable disease: best buys, wasted buys, and contestable buys. *BMJ*. 2020:368:m141. https://doi.org/10.1136/bmj.m141

5. HiTAP website. Accessed July 27, 2022/. https://www.buyitbestncd.health/

6. Sharma M, Teerawattananon Y, Dabak, et al. A landscape analysis of health technology assessment capacity in the Association of South-East Asian Nations region. *Health Res Policy Sys*. 2021;(19):19. https://doi.org/10.1186/s12961-020-00647-0

7. Husereau D, Drummond M, Augustovski F, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Explanation and Elaboration: A report of the ISPOR CHEERS II Good Practices Task Force. *Value Health*. 2022;25(1):10-31.

8. Cookson R, Griffin S, Norheim OF, Culyer AJ. *Distributional Cost-Effectiveness Analysis Quantifying Health Equity Impacts and Trade-Offs: Quantifying Health Equity Impacts and Trade-Offs.* Oxford, UK: Oxford University Press; 2020.

9. Rumbold B, Baker R, Ferraz O, et al. Universal health coverage, priority setting, and the human right to health. *Lancet*. 2017;390:712-714. https://doi.org/10.1016/S0140-6736(17)30931-5

10. Love-Koh J, Cookson R, Gutacker N, Patton T, Griffin S. Aggregate distributional cost-effectiveness analysis of health technologies. *Value Health*. 2019;22(5):518-26.

11. Dawkins BR, Mirelman AJ, Asaria M, Johansson KA, Cookson RA. Distributional cost-effectiveness analysis in low- and middle-income countries: illustrative example of rotavirus vaccination in Ethiopia. *Health Policy Plan*. 2018;33(3):456-463.

12. Verguet S, Gauvreau CL, Mishra S, et al. The consequences of tobacco tax on household health and finances in rich and poor smokers in China: an extended cost-effectiveness analysis. *Lancet Glob Health*. 2015;3(4):206-216. https://doi.org/10.1016/s2214- 109x(15)70095-1

13. Non-communicable diseases. World Health Organization website. Published 2018. Accessed July 26, 2022. https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases

14. 10 Factors on Mental Health. World Health Organization website. Published 2019. Accessed July 27, 2022. https://www.who.int/features/factfiles/mental_health/mental_health_facts/en/index1.html

15. Verguet S, Laxminarayan R, Jamison DT. Universal public finance of tuberculosis treatment in India: an extended cost-effectiveness analysis. *Health Econ*. 2015;24(3):318-332.

16. Lou J, KC S, Toh YK, et al. Real-world data for health technology assessment for reimbursement decisions in Asia: current landscape and a way forward. *Int J Technol Assess Health Care*. 2020;36:474-480. https://doi.org/10.1017/S0266462320000628

ISPOR

Improving healthcare decisions

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