VALUE & OUTCOMES SPOTLIGHT

A magazine for the global HEOR community.

NAVIGATING THE PUBLISHING LANDSCAPE

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

In a world inundating us with information through emails, social media posts, virtual meetings, conference calls, television, paper media, and (hopefully soon) in-person interactions, an implicit expectation is that, ironically, humans can process information at the same pace as the platforms being used to deliver these communications. This plethora of communication forums can be frustrating—and at times, overwhelming to their consumers who do not have the time or the capacity to digest the glutony of information served to them!

The gallimaufry of chimerical data, rumor, opinion, conspiracy, and unsubstantiated conclusion can muddle scientific facts, truths, and corroborated results. In this communication maelstrom, how can we as health economics and outcomes research (HEOR) professionals communicate simply and effectively when the messages we convey are often complex and science-heavy and experience a time lag due to rigorous review required by the organizations for which we work and/or the media outlets through which we communicate? How can we maximally propagate our work so that it reaches the broadest audience and does not end up at the bottom of their “digital pile”? Is there value in the potential tradeoff between a rapid, nonpeer-reviewed publication and a longer-term peer-reviewed publication? If an open access peer-reviewed platform is chosen, then who will be responsible for paying the publication fee?

Given the increased importance and accumulating volumes of metadata utilized in explaining and validating clinical and economic outcomes, can we use sophisticated computational algorithms to reduce the human burden of conducting systematic literature reviews, formal meta-analyses, and indirect treatment comparisons while maintaining the quality of the data and conclusions?

Indeed, it is one thing to execute these studies but quite another to communicate the findings and conclusions—yet both are essential to our science and ultimately the success of our profession. Communication challenges existed well before the COVID-19 pandemic but have multiplied as a result of increased reliance on digital communications.

In this issue, we feature the frontiers of the rapidly evolving HEOR publishing landscape: (1) the movement towards open access scientific publication, which directly impacts Value in Health and other high-impact journals in our space; (2) preprint portals that serve as rapid but potentially controversial mechanisms for publishing our work that typically occurs without peer review; and (3) use of metatools that generate “evidence on the evidence” by culling through established portals such as PubMed and clinicaltrials.gov and creating automated summaries of existing publications.

Given the myriad options available to us for HEOR publishing, we should leverage these opportunities to navigate the changing publishing landscape and choose the path that best meets our purpose!

Zeba M. Khan, RPh, PhD and Laura T. Pizzi, PharmD, MPH
Editors-in-Chief, Value & Outcomes Spotlight
ISPOR’s Science Strategy: A Multiyear Blueprint
Richard J. Willke, PhD, Chief Science Officer, ISPOR, Lawrenceville, NJ USA

ISPOR’s Science Strategy, released in the first quarter of 2021 as a directive in ISPOR’s Strategic Plan Update 2024, is a multiyear blueprint that will guide the Society’s efforts and mission-focused initiatives. The objective of the ISPOR Science Strategy is to identify a targeted set of topical “themes” and focal points for research that the Society believes will have the greatest impact on both the field of health economics and outcomes research (HEOR) and global healthcare. The intention is that this strategy can be leveraged to advance the science, drive innovation in the field, and have an even greater impact on improving healthcare decisions.

The development of ISPOR’s Science Strategy was heavily informed by its members. As a member-driven organization, the Society relies on member input to guide all that it does. The first step in development of the Science Strategy was to gather topic suggestions by conducting a comprehensive survey of the members of the Society’s various groups, including its councils, special interest groups, board of directors, regional and student chapters, editorial boards, current and former task forces, etc. This initial survey resulted in 908 suggestions from members of 122 member groups representing more than 45 countries. The subsequent work to synthesize and summarize these research topics was led by ISPOR’s most senior advisory body, the Health Science Policy Council, and was approved by ISPOR’s Board of Directors in the Fall of 2020. ISPOR is most grateful to its membership for the robust response to this effort. Members’ enthusiasm for progressing the science of HEOR is clear.

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The Science Strategy provides direction in 8 different themes of HEOR science and application, outlined below. It covers most key areas of HEOR work, while calling out specific areas of focus in each theme—these focal points are outlined in the Figure. It is also important to note that while the Science Strategy is expected to define the greater part of ISPOR’s coming activities, new ideas are always welcomed and will certainly arise.

Real-World Evidence: Make HEOR evidence based on real-world data credible and reliable for use in healthcare decision making. The great potential for use of real-world data in healthcare research and decision making remains limited due to concerns about data quality, ability to discern causality, the transparency and reproducibility of the research process. While excellent progress has been made in each of these areas, that progress has not yet led to good practices becoming common practices, or to a broader understanding of under what circumstances (and for what purposes) evidence derived from real-world data can be trusted.

Economic Evaluation Methods: Stimulate methodological innovation in health economic evaluation and value assessment to better capture the complexities of new technologies and healthcare processes. The core methods of health economic evaluation are generally well established but may not reflect some important considerations that affect real-world decision making. For example, there are important insights from behavioral economics, more complex clinical pathways with treatment sequences and other trajectory modifiers, societal values that embrace dimensions beyond those in the standard quality-adjusted duration of life, and novel therapies that may be curative. In addition, understanding of the importance of variation—due to heterogeneity or residual uncertainty, including structural—has advanced, but methods for factoring that variation into such evaluations are just beginning to develop.

Patient-Centered Research: Refine the measurement of patient- and proxy-reported outcomes and preferences to improve their veracity, rigor, and usefulness for healthcare decisions. There are still major gaps in the availability of standardized clinical outcomes that are meaningful to patients and/or patient- (or proxy-) reported outcomes that produce evidence relevant both for health state utilities for economic evaluation and for healthcare decision making in general, particularly for special populations (eg, children, chronically disabled). Stated-preference research can be used to evaluate the relative importance of dissimilar treatment features and health outcomes and provide empirical evidence to inform value judgments.

Special Populations and Technologies: Identify innovations and adaptations of HEOR methods that target selected areas of disease management and decision making (eg, rare disease, precision medicine, etc). Special populations and technologies are defined as those with unique features that pose particular challenges for evidence generation, health technology assessment (HTA), economic evaluation, and outcomes research. Examples include treatments for rare diseases, gene therapies, biosimilars, medical nutrition, and digital health monitoring, among others.

HTA in Healthcare Decision Making: Identify approaches that strengthen the linkage between HTA and healthcare decision...
making to improve the efficiency, transparency, and fairness of both. HTA has the potential to play an integral role in healthcare decision making. In practice, it often has less impact than expected. Strengthening the connection between HTA and healthcare decision making should enable HTA to reach this potential. Appropriate institutionalization of HTA, a greater degree of participation by different stakeholders, and improved transparency in the HTA process (as well as the criteria used by the decision makers) can improve the efficiency, transparency, and perceived fairness of this process.

ISPOR’s Science Strategy is intended to help inform and guide our content strategies and member group activities for the next several years.

**Health Economics, Access, and Policy**: Develop health economics and HTA tools that apply to health policy, research and development, pricing, and reimbursement to optimize and balance the needs of access, sustainability, and innovation. Given patents and data exclusivity, how should products be priced to ensure the maximum access compatible with providing the maximum long-run health gains from innovation? Cost-effectiveness analysis remains a standard but much-debated approach to assessing value and determining prices. To better capture some aspects of value, a number of modifications to cost-effectiveness analysis have recently been suggested but need further exploration and testing. Separate from—but related to—pricing is coverage and reimbursement by a payer, where there are a wide variety of coverage paradigms across payers/countries as well as across types of drugs (eg, orphan drugs or accelerated approvals).

**Low- and Middle-Income Countries**: Promote HEOR methods and resources that support HTA across the diverse range of health systems including low- and middle-income countries. As more countries move toward a universal healthcare coverage model, prioritization within limited budgets is paramount. HEOR methods can be used and adapted in many different types of healthcare systems to help facilitate and align priority setting across all aspects of a health delivery system, regardless of the stage of the country’s development. However, these methods are only helpful if there is synergy across problem definition, evidence generation, and decision making. Compounding this

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**Figure. Focal points for Science Strategy theme areas.**

<table>
<thead>
<tr>
<th>Real-World Evidence</th>
<th>Special Populations and Technologies</th>
<th>Health Economics, Access, and Policy</th>
<th>Low- and Middle-Income Countries</th>
<th>Resilient, Learning Healthcare Systems</th>
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<tbody>
<tr>
<td>Develop criteria for evaluating the research readiness of real-world databases</td>
<td>Designs for studies to generate evidence for rare diseases therapies</td>
<td>Address international pricing issues to incentivize research and development globally, while promoting low- and middle-income country access</td>
<td>Develop best practices for prioritization of assessment criteria and HTA capacity building</td>
<td>Review and address the HEOR methods and data gaps highlighted by the COVID-19 situation</td>
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<td>Conduct further research into causal inference techniques and replicating randomized clinical trial results</td>
<td>Methods to evaluate the value of, and novel payment methods for, very high-cost curative therapies</td>
<td>Test the use of novel elements of value in value-based pricing in real-world situations</td>
<td>Build regional adaptation capabilities through sharing of HEOR methodologies</td>
<td>Assess other known trends (eg, environmental) to consider what HEOR methods and data are needed</td>
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<tr>
<td>Enable researchers to follow good practices for real-world data study protocol registration and reproducibility</td>
<td>Pricing and reimbursement for personalized medicine tests and biomarkers</td>
<td>Test performance-based risk-sharing and other innovative pricing/coverage agreements</td>
<td>Advance the methods involved in valuation of life across regions</td>
<td>HEOR indicates health economics and outcomes research; HTA, health technology assessment.</td>
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<tr>
<td>Broaden the capture of elements of value beyond the quality-of-life-years and of broader societal costs</td>
<td>Frameworks and best practices for evaluation and assessment of digital healthcare</td>
<td>Explore how budget impact, affordability, and value sharing are best addressed</td>
<td>Develop best practices for prioritization of assessment criteria and HTA capacity building</td>
<td>For the complete versions of these focal points, please see the original Science Strategy.</td>
</tr>
<tr>
<td>Address heterogeneity of treatment effect and data limitations on outcomes measurement</td>
<td>Best practices for comparing cost-effectiveness of biosimilars</td>
<td>Test the use of novel elements of value in value-based pricing in real-world situations</td>
<td>Build regional adaptation capabilities through sharing of HEOR methodologies</td>
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issue is that most HTA systems, structures, and standards are generally driven by developed countries. Thus, there is a need to better understand the applicability and sustainability of HEOR approaches especially for low- and middle-income countries.

HEOR, as a blend of social, healthcare, and data sciences, provides a framework that can clearly define healthcare issues and generate the relevant evidence to inform healthcare decision making.

Resilient, Learning Healthcare Systems: Develop HEOR methods and applications that contribute to resilient, learning healthcare systems. Healthcare systems are intertwined with many other aspects of how we live and how society functions—our economy, our environment, our demographics, our legal system, etc. The COVID-19 pandemic has highlighted the interconnectedness of health, public health, and the larger economy. To inform decisions that may have cross-sector ramifications, HEOR researchers should broaden their perspectives to include nonhealth-related outcomes, such as effects on the larger economy, educational outcomes, housing, and social welfare. We should also seek to collaborate with other disciplines that provide complementary perspectives and methods that will help us address these issues more comprehensively.

ISPOR’s Science Strategy is intended to help inform and guide our content strategies and member group activities for the next several years. ISPOR will incorporate Science Strategy elements into its business plans, content strategies, discussions, and program themes. It is also meant to inform the Society’s stakeholders and the broader healthcare audience about current areas of interest for both ISPOR and the global HEOR community. We highly encourage its use for discussions and coordinated activities across ISPOR member groups.

The need has never been greater for HEOR to inform healthcare decisions. Healthcare’s myriad challenges—the COVID-19 pandemic, the growth of innovative (but expensive) curative therapies, the move toward universal healthcare, the need to provide optimal health outcomes for patients within budget constraints, to name a few—combined with the increasing complexity of healthcare—bring the demand for HEOR to the forefront. HEOR, as a blend of social, healthcare, and data sciences, provides a framework that can clearly define healthcare issues and generate the relevant evidence to inform healthcare decision making. If well-focused on today’s healthcare challenges, HEOR has the potential to markedly improve societal well-being and make a real impact in the lives of patients.
1 Factors Associated With Prescriptions for Branded Medications in the Medicare Part D Program
(JAMA Network Open)
A cross-sectional study of 169 million Medicare Part D multisource prescription drug claims in 2017 revealed that branded dispensing of multisource drugs requested by prescribers or patients was associated with increased spending for the Medicare program and patients. Switching the branded drugs requested by prescribers to generics would have saved $997 million for Medicare and $161 million for patients. Read more.

2 Inside the Fall of Watson Health: How IBM’s Audacious Plan to “Change the Face of Healthcare” With Artificial Intelligence Fell Apart
(STAT News)
A STAT investigation found that the downfall of Watson Health was driven by a series of self-inflicted wounds that mounted over years of overheated marketing and underperforming products. Internal documents and interviews with former employees and industry collaborators point to a corporate leadership that prioritized publicity and short-term financial goals over the plodding work of science and building the kind of business that could outlast its early hype. Read more.

3 NICE Says No to AstraZeneca’s Lynparza (olaparib) for Prostate Cancer
(pharmaphorum)
Draft guidance from the National Institute for Health and Care Excellence (NICE) in March has ruled out patients in England using lynparza if they have BRCA-positive advanced prostate cancer. AstraZeneca was seeking to use the PARP inhibitor in patients who had also been previously treated with docetaxel, but NICE concluded that the application failed to provide evidence of the value of lynparza compared to standard therapy. Read more.

4 Cornerstones of “Fair” Drug Coverage: Appropriate Cost Sharing and Utilization Management Policies for Pharmaceuticals
(Future Medicine)
The Institute for Clinical and Economic Review's (ICER) Steven Pearson, Maria Lowe, and Steven S. Segal, together with Adrian Towse and Chris Henshall of the Office of Health Economics, London, England, United Kingdom, put out a white paper that sets design criteria to determine whether insurance coverage is providing fair access to drugs through cost sharing, clinical eligibility criteria, and step therapy. Read more.

5 A Nascent State Effort Would Tax Drug Makers for Not Providing Clinical Evidence for Price Hikes
(Pharmalot)
Hawaii and Washington recently introduced bills that would tax drug makers for raising prices without providing clinical evidence to justify the increases. Although the bills failed to gain traction, experts say the ongoing state initiatives underscore the intractable nature of the problem of drug price increases. Read more.

6 Novartis’ £1.79M Gene Therapy Zolgensma (onasemnogene abeparvovec-xio) Scores Cost Watchdog’s Backing, Threatening Biogen’s Spinraza (nusinersen)
(Fierce Pharma)
NICE has endorsed Novartis’ gene therapy zolgensma in a draft guidance which, if finalized, would make the medication the most expensive drug ever to be approved by the cost-effectiveness agency. Because zolgensma is a “potentially curative one-off gene therapy” that can provide “exceptional benefit” to patients, NICE reviewers concluded it is worth the high cost in certain patients. Read more.

7 Targeting of the Diabetes Prevention Program Leads to Substantial Benefits When Capacity Is Constrained
(Acta Diabetologica)
A study by Tuft’s Natalia Olchanski, David Klaveren, John B. Wong, Robin Ruthaven, and David M. Kent published in Acta Diabetologica in January found that targeting active diabetes prevention to patients at highest risk could improve health outcomes and reduce costs compared to providing the same intervention to a similar number of patients with prediabetes without targeted selection. Read more.

8 Research Update: Center for Enhanced Value Assessment
(CEVR)
Tuft’s Center for the Evaluation of Value and Risk in Health (CEVR) put out an update about its Center for Enhanced Value Assessment project, which turned 2 years old in February. CEVR is “exploring salient elements of value in and alongside traditional cost-effectiveness analyses.” The center published several papers in 2020 including, “Measuring ‘Fearonomic Effects’ in Valuing Therapies: An Application to COVID-19 in China,” in the November 2020 issue of Value in Health. Read more.
Opportunities to Advance Real-World Evidence in Europe: Assessing Today’s Landscape and Priorities for Future Guidance
(Aetion)
Aetion’s Ashley Jackson and Nicolas Deltour talk about the real-world evidence (RWE) landscape in Europe, how platforms can support stakeholders in running credible analyses, and what more is needed from regulators and health technology assessment bodies to advance RWE.
Read more.

Opinion: To Really Lower Healthcare Costs, Look Beyond Prescription Drugs
(Washington Post)
Harvard Medical School’s Anupam P. Jena writes in the Washington Post about why the policy focus remains on high drug prices in the United States and what can be done to more openly assess the impact of other costs that actually make up more healthcare spending, such as doctors’ services and hospital care. While there are plenty of high-quality data about drug costs, there are no high-quality data on whether certain hospitals or doctors are better than others, and no good evidence on whether many of the services that hospitals or doctors provide are really needed.
Read more.

New Developments in HTA: Evolution Not Revolution in Health Technology Assessment
(Economist Intelligence Unit)
In a new report, researchers at the Economist Intelligence Unit describe the new and emerging developments in HTA, the developments that will be seen in the near future, and how HTA is not a static endeavor, but one that must evolve if it is to overcome the challenges identified.
Read more.
Assessing the Added Therapeutic Benefit of Ultra-Expensive Drugs


Added therapeutic benefit (ATB) assessment relies on gauging the value of a drug or technology through improvement in patient-relevant endpoints. Valuation of medical technologies and drugs guided by assessment is often a first step in the reimbursement process. It could present an alternative to cost-effectiveness analysis for jurisdictions where it is not acceptable, as it is less tied to income and willingness-to-pay levels.

Adoption of the ATB assessment to inform the reimbursement and pricing process becomes relevant especially in the case of extremely expensive drugs, which can lead to a significant cost burden for the payers. This paper examined the added therapeutic benefit of the most expensive drugs prescribed to Medicare Part D beneficiaries in the United States by utilizing publicly available ATB ratings from the health technology assessment agencies in France, Germany, and Canada. These countries have similar gross domestic product to the United States, and ATB ratings are assigned independent of the drug price and the therapeutic benefit compared to the current standard of care. The factors considered in ATB assessments across the 3 countries were (1) quality of research evidence; (2) improvement in efficacy; (3) clinical relevance; (4) assessment of innovation; (5) patient and caregiver convenience; and (6) reduction in incidence and side effects, among others.

Drugs were considered “ultra-expensive” when the average annual per beneficiary spending by Medicare Part D program in the United States was greater than the per capita gross domestic product of the United States in 2018 ($62,794). This threshold is somewhat arbitrary but is only used by authors to select the therapies that they later analyze from the perspective of ATB.

As a result of the varying rating mechanisms across France (5 levels of ATB: major, important, moderate, minor, and none), Canada (4 levels of ATB: breakthrough, substantial, moderate, and slight/none), and Germany (6 levels of ATB: major, considerable, minor, nonquantifiable benefit, none, and less) a binary variable was created that collectively classified the top 2 levels in each of the countries as “high ATB” and the rest of the levels were defined as “low ATB.”

A modification to this variable was made for Canadian assessments conducted prior to 2010 as they had defined only 3 levels of ATB (breakthrough or substantial, moderate/little/no, and a line extension). Drugs classified as breakthrough or substantial were termed by the authors as “high ATB” whereas the remaining were categorized as “low ATB.”

A total of 122 drugs were defined as ultra-expensive, 79% of which were approved as orphan drugs in the United States with an average amount of $174,669 annual spent per Medicare beneficiary. Not all of these were assessed internationally: 60% were assessed in France, 45% in Canada, and 35% in Germany (Figure). More than 70% of the drugs assessed in France (85%), Canada (73%), and Germany (74%) received a low ATB rating. Around 93% of drugs analyzed within 1 country and 61% of drugs assessed in either 2 or all 3 countries were classified as contributing low ATB in comparison to the existing standard of care.

None of the drugs evaluated in all the countries were rated as high ATB. There was a high agreement in scoring between France and Canada (85%), followed by Canada and Germany (69%), and France and Germany (67%). Around 67% of the assessed drugs in France and Canada, 62% in Canada and
Germany, and 67% in France and Germany were always rated as low ATB (ie, there was relatively consistent assessment across countries. None of the drugs were always rated as high ATB in France and Germany). Despite the low ratings of many drugs, the per capita Medicare spending for each is high, indicating that a substantial proportion of the spending covers for drugs with low ATB. The authors were especially concerned that over 70% of the drugs assessed in the study were categorized as orphan and were priced at a much higher rate but offered a lower ATB in comparison to the likely much less expensive standard of care.

This paper highlights a potential first step towards value-based pricing in the United States: ATB assessment does not depend on the quality-adjusted life-year or the use of a value threshold, it may be more politically acceptable than cost-effectiveness analysis. Although the implementation of ATB and its position along the reimbursement pathway is different across the 3 countries (eg, pre- or postmarket entry), the authors suggest that the ATB assessment of either Germany, France or Canada could serve as a proxy until there are US-specific ATB criteria.

With the number of ultra-expensive therapies growing and the proportion of public health expenditure spent on these increasing, there is a greater need for resource allocation decisions that may be potentially more equitable and could provide care for more patients in the United States. The authors present some convincing arguments as to why it may be time to consider examples, even when cost-effectiveness analysis is not politically desirable.
ISPOR NEWS

Quality, Access, and the Use of Real-World Data by Payers: Where Are We Now? Where Do We Want to Be in the Future?

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One of the biggest challenges payers face today is determining the value of innovative therapies in diseases with high unmet medical needs, such as cancer and rare diseases. These novel therapies show promise, but there is often significant uncertainty regarding their added value to patients and their cost to the healthcare system. In some cases, the new therapies front-load most of the cost as is seen with gene and cell therapies. This creates strain on healthcare system budgets, raises affordability and equity issues, and challenges decision making by health technology assessment (HTA) bodies and payers. Some payers are addressing this challenge by providing conditional reimbursement and employing risk-sharing strategies via managed entry agreements (MEAs). Although most MEAs promise predictable budget impact, there is also a move towards the development and application of performance- or outcomes-based MEAs. To support the implementation of outcomes-based agreements, HTA bodies and payers are increasingly looking to collect and analyze real-world data (RWD).

Barriers to Overcome
The ISPOR Payer Summit was developed in collaboration with a group of dedicated volunteers representing a cross-section of stakeholders. The Summit was an invitational, multistakeholder event to discuss the use of real-world evidence (RWE) by public and private payers in the United States and Canada. The Summit was moderated by Clifford Goodman, PhD, Senior Vice President, Comparative Effectiveness Research, The Lewin Group, Falls Church, VA, USA. It began with expert summaries of 2 prerecorded presentations from Sebastian Schneeweiss, MD, ScD, Harvard Medical School, Boston, MA, USA, and Francesca Cunningham, PharmD, Director of the Center for Medication and Safety at the US Department of Veterans Affairs, Hines, IL, USA.

Dr Schneeweiss highlighted some of the barriers that payers face in using RWE. He noted, “Payers make high-impact healthcare decisions all the time, yet they underutilize their very own data to identify what works in their population. They often have little confidence in RWE and lack capacity to produce it at scale in real time with their own data.” However, he suggested the use of modern rapid-cycle analytic platforms can help overcome these barriers. Schneeweiss proposed the use of a Meaningful, Valid, Expedited, and Transparent evidence framework (MVET framework) 1 to instill confidence in using RWD for decision making. He presented several examples, including a study that showed improved health outcomes and total cost of care when using SGLT-2s in high-risk cardiovascular disease patients with diabetes based on data from the very population that the health plan manages rather than an external finding. 2 “While there are some considerations involved in using RWE to support reimbursement decisions, the benefits are significant. Without the use of RWE, payers are left with making substantial extrapolations from randomized controlled trial evidence,” Schneeweiss said.

Using Data for Better Patient Outcomes
Dr Cunningham discussed several ways that the US Department of Veterans Affairs (VA) uses its data to better understand safety and effectiveness outcomes for its patients. She highlighted some of the decisions made in real time using VA databases, data warehouses, and electronic health records (EHRs), together with an assortment of dashboards. She explained that the VA uses RWD in many ways: (1) to conduct active and passive safety surveillance; (2) to support national medication use evaluations (MUES); (3) to populate risk reduction dashboards; (4) to inform formulary management, including responses to complex queries and traditional formulary decisions; and (5) to develop research proposals.

Ideally, the future of using real-world evidence for coverage decisions requires clearly defined terminology and processes to broadly integrate data (including patient-generated data).

Cunningham presented one example that focused on COVID-19 and the ability of the VA to evaluate and characterize utilization of diagnostic testing and various treatments for the virus. This allowed them to provide pertinent and timely information, including detailed safety monitoring of medications to decision makers and healthcare providers. She also provided background on their evaluation of several potential therapies proposed to treat patients during the pandemic. Using a lesson learned approach, the VA identified several areas to improve the use of RWD such as: (a) the need to enhance database connectivity and interoperability; (b) a requirement to develop new methods and tools to address different types of questions; (c) and a need to efficiently capture data and develop the tools necessary to answer the question at hand. She stressed the importance of understanding the limitations of administrative data and highlighted the benefits of developing tools to enhance the use of data.

The participants were then divided into 4 discussion groups. Two groups focused on the current landscape of using RWD in coverage decisions, and 2 groups focused on the future landscape. Participants were asked to answer the following questions:
Current landscape

“What is the current landscape of using RWD in coverage decisions? What is preventing impactful use of RWD/RWE in the current environment by payers?”

Future landscape

“What does the ‘ideal’ future of using RWD/RWE in coverage decisions look like? Where do we want to be? How do we get there (the future ideal)? What big changes, collaborations, or data linkages would have to take place?”

Results From the Current Landscape Breakout Groups

While most agreed that more could and should be done with RWE in payer decision making, most of the barriers discussed that are preventing further application of RWE are not new—they involve many of the same challenges discussed for many years. Where there is use of RWD, it is still unclear how it is informing decisions in real time. Current usage of RWE includes developing prior authorization criteria and supporting appeals (including how the process has changed over time), new data collection to supplement HTA or to reassess technologies, exploratory or population-level health management including disease state information (often for orphan diseases), conditional reimbursement and value-based agreements, and reporting of patient experience particularly for specialty pharmacy products.

Results From the Future Landscape Breakout Groups

Ideally, the future of using RWE for coverage decisions requires clearly defined terminology and processes to broadly integrate data (including patient-generated data). RWD should be used by regulators and HTA bodies to conduct rolling reviews and to “evergreen” technology assessments. These reassessments can then be used to modify reimbursement criteria, renegotiate prices, and eventually to support disinvestment decisions.

To gain the confidence of payers and other stakeholders, these data must be of high quality, replicable, robust, and transparent and should include the most relevant variables and adequate sample sizes. Participants felt that RWD should ideally be used to translate clinical trial efficacy into relevant real-world effectiveness and cost-effectiveness on a routine basis, as well as to monitor real-world effectiveness over time. There should be an ongoing data stream with real-time “dashboard” analytic capabilities to query and report data as needed by payers and providers, perhaps using predefined algorithms and artificial intelligence platforms. There should be processes to enhance communication amongst stakeholders about product or service performance. This will also require an underlying knowledge and acceptance of the quality and relevance of RWE by end users and how best to put it into context of the data continuum. A collaborative approach to research and an ability to leverage capabilities from different stakeholders is also required.

How Can ISPOR Support “Current Landscape” Groups?

- Enhancing the use of RWE:
  • Producing practice guidelines
  • Providing technical training for payers and other stakeholders
  • Developing tools to integrate RWD into their decision-making processes

- Creating standardized definitions of clinical outcomes focused on relevant information to patients and payers

- Sharing successful cases and best practices:
  • Publishing examples and demonstration projects

- Engaging providers in building clinical practice guidelines and care pathways based on RWE/RWD

- Support the use of patient-generated health data (to fill knowledge gaps and capture data outside of traditional clinical practice)

- Support the use of social determinants of health and disparity in decision-making processes

How Can ISPOR Support “Future Landscape” Groups?

- Supporting the creation of data linkages and universal patient identifiers will enhance the creation of robust “all-inclusive” datasets

- Promoting the development of network data pool based on open data platform, available to all key stakeholders

- Stimulating the realignment of incentives and priorities to:
  Develop and maintain platforms
  Manage the input of data
  Data analysis and storage
  Build real-time analytics and end-user capabilities to interpret the results

You Can Get There From Here

So, how do we get there? Data linkages and universal patient identifiers will enhance the ability to create the robust all-inclusive datasets envisioned by this ideal future. In addition, a networked data pool (pond, lake, ocean), similar to the US Food and Drug Administration’s (FDA’s) Sentinel initiative, based on an open data platform that is available to all key stakeholders will be beneficial. This will require a realignment of incentives and priorities as well as resources to develop and maintain the platforms, manage the input of data, download and analyze the data, and build real-time analytics and end-user capabilities to interpret the resulting output.
How Can ISPOR Help?
ISPOR brings together many different perspectives and stakeholders in industry, regulators, HTA agencies, payers, providers, academics, and patient groups that will be instrumental to solving some of the challenges raised in this summit. Certainly examples, guidance, and tools for implementing RWE in decision making are ways that ISPOR has and will continue to make a difference in this space. But education and training of relevant and competent RWE data scientists, epidemiologists and outcomes researchers cannot be underestimated. Developing a competency framework for these experts in training will be essential, while also continuing to provide training opportunities through short courses, webinars, and event workshops.

Some specific points ISPOR can address going forward include:

1. **Promote collaboration among stakeholders (industry, regulators, HTA agencies, payers, providers, academics, and patient groups)**
   One of the powers that a professional association like ISPOR possesses is the ability to promote interaction and collaboration among stakeholders. The safe havens provided by meeting together outside of the promotional space allows for constructive dialogue on topics that impact all participants, including ideas and recommendations on how to work collaboratively to move beyond the barriers identified.

2. **Provide education and training**
   ISPOR, as a global scientific and educational organization for health economics and outcomes research, is well positioned to offer training related to RWE. Understanding that the capacity to analyze and interpret data in this context is at a premium, ISPOR can create opportunities for payers, clinicians, researchers, and patients to enhance their knowledge in the application of RWE.

3. **Disseminate RWE case studies, guidance documents, and tools to promote broad adoption**
   ISPOR should gather actual examples of RWE use in coverage decisions. These examples can help identify opportunities and challenges to the use of RWE in decision making. ISPOR can also work with experts and stakeholders to develop guidance documents and tools to harmonize approaches to the collection and use of RWE and to contextualize RWE use based on local needs. This will require a concerted effort by all stakeholders to bring together the various “data owners” (companies, private and government insurers, academic data aggregators, and patient organizations). ISPOR can help support the creation of these linkages.

4. **Champion RWE initiatives that incorporate patient perspectives**
   ISPOR works with individual patient representatives and patient groups to ensure that the patient voice remains a key input to market access, and that should include how RWE is employed in coverage decisions. Patients are generating healthcare data through their interactions with providers and insurers. However, the increased use of data from wearables, healthcare apps, and other social media-derived datasets is becoming increasingly integral to this discussion. Patients and patient groups need to be directly involved in the effort to increase the acceptance of patient-generated data. ISPOR remains committed to elevating patient involvement in these initiatives.

**References**
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- All session recordings available until June 30, 2021.

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- Live programming for 3 days with virtual poster presentations, networking opportunities, a virtual exhibitor gallery, and access to postconference recordings for a full month after the event.

Once it is determined safe to return to in-person gatherings (dependent on pandemic status), those sessions will be added to the overall conference. Announcements regarding possible in-person sessions will be determined later this year.

Notable Dates:

<table>
<thead>
<tr>
<th>Call for Abstracts:</th>
<th>Submission Deadlines:</th>
<th>Notifications:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Issue Panels and Workshops</td>
<td>8 April</td>
<td>10 June</td>
</tr>
<tr>
<td>Research</td>
<td>4 May</td>
<td>29 June</td>
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</table>

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The course will be taught by Theresa Coles, PhD, Duke University, Durham, NC, USA.

Learn more and register for ISPOR Short Courses: [www.ispor.org/shortcourses](http://www.ispor.org/shortcourses)

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Now is the time to engage with ISPOR's growing network of influential HEOR leaders to promote HEOR excellence and improve decision making for health globally. *Partner with ISPOR today!* Explore exhibit and sponsorship opportunities [here](http://www.ispor.org/).
An increasing number of stakeholders rely on health economics and outcomes research (HEOR) evidence to assess relative value, to weigh treatment choices, and to help them target possible patient outcomes under finite budgets. Clinicians, payers, patients, governments, health ministries, and other stakeholders are utilizing HEOR research to inform their understanding of the therapeutic and economic value of a given product in a real-world clinical practice environment and to help clarify their decision making. These parties need access to up-to-date HEOR information, such as real-world patient outcomes data, quality-of-life surveys, opportunity costs of various treatment mixes, budget impact studies, and cost-effectiveness models.

In this article, Johan Rooryck, PhD; Michael F. Drummond, MCom, DPhil; Rick Anderson, MLIS; and Richard White, PhD, shared their thoughts on changes to scholarly publishing, including preprint portals, open access, and their impact on the effective dissemination of HEOR.
The HEOR publishing environment is evolving to help meet the demand for more timely access to HEOR evidence with new journals, open access publications, and preprint servers. The explosion of preprint servers and different open access models have changed scientific publishing, recreating the standard for disseminating time-critical research and expanding access to researchers, practitioners, policy makers, patients, and the public. Coupled with newer HEOR journals and HEOR-cognizant reviewers, HEOR researchers face expanding options to share their findings.

Many policy makers are supporting these changes in scholarly publishing. While the United States still lags behind Europe and other countries, such as South Africa, in requiring open access to research derived from government-funded research, this may soon change. In United States, the Trump administration considered enacting an executive order in early 2020 that would mandate open access to federally funded research. As the critical importance of broad and timely access to scientific evidence was supported by the lightning speed of COVID vaccine development, the new Biden administration may soon implement a similar order despite continued pushback from the publishing community, further solidifying these important changes to scholarly publishing.

**Changing a Centuries-Old Publishing System**
For roughly 300 years, researchers have relied on publishers to disseminate literature through a rigorous peer-review process funded by subscriptions. While this model provides the structure to identify rigorous research, it also slows the dissemination of critical research and limits access to libraries, subscribers, and readers covered by a site license. To ensure free and ready access to timely research, scientific publishers are being pushed to change their publishing models from the traditional subscription model to models that promote “open science,” like preprint servers and open access publishing.

**Preprints Expedite Research Dissemination**
Preprints (see related article by Cohen, et al, in this issue) are the original versions of publications submitted for review. They may be accessed online by anyone at no cost before (and sometimes after) the work has been published. They are released without peer review, thus cutting months from time to dissemination. Preprints can also help researchers disseminate their findings quickly. Like the open access platforms, preprints have become a rapidly growing option, spurred in part by COVID-19–related materials.

Richard White, MA PhD, Chief Operating Officer, Oxford PharmaGenesis, Oxford, Oxfordshire, UK, argues that preprints could be an attractive option for some types of studies funded by the pharmaceutical industry, sometimes in lieu of a press release as the first point of data dissemination and as an antecedent to a manuscript. The flexibility of preprints may better accommodate the dynamic nature of HEOR. “I think they’re potentially valuable. The challenge with HEOR studies is that flex in the methodology and evolution of results.” He continued, “When you do a randomized controlled trial, it’s all very clear what the protocol is. If you’re doing an economic model, there’s some scope for latitude based on what inputs are actually available.” He notes how some data in economic models may be derived from expert opinion, which may be prone to changes, and many HEOR studies derive results from dynamic, real-world datasets. “There could be merit in preprints having that ability to shape the research a little bit as we’ve seen in the physical sciences.”

Michael Drummond, MCom, DPhil, Centre for Health Economics, York University, York, Yorkshire, UK (and Editor-in-Chief of Value in Health), supports preprints for promotion. However, he warns that he would not recommend the preprint route for junior academic colleagues. For younger academics, a robust publication record in highly reputable journals still drives tenure decisions; preprints provide limited value to these researchers.

**Risks of Preprints and Predatory Journals**
Rick Anderson, MLIS, University Librarian at Brigham Young University, Salt Lake City, UT, USA, and contributor to the Scholarly Kitchen, provided some critical insight into the challenges surrounding preprints, article processing charges, and open access publishing.

Given the lack of peer review, Anderson warns that preprints can be targeted by bad actors pushing poor research onto preprint servers to tout results as having been published. He noted this problem is often compounded by a credulous journalistic community that may not fully understand the subtleties of scholarly publishing, citing preprint findings as if they were from a peer-reviewed journal. The journal Nature has warned the scientific community that measures must be taken to keep preprints from distorting the public’s view of scientific research, highlighting the problematic dissemination of a (now retracted) paper reporting that genetically modified corn caused cancer in rats. In some cases, challenges may exceed poor scientific methodology and encroach on fraud, including false affiliations and fake authors. Anderson himself participated in sting operations, successfully publishing a fraudulent paper with fake authors, which is still online.

It’s so important to get the science out there quickly and publicly, but on the other hand, there’s so much danger in putting bad science out quickly and publicly. All of the benefits are exactly mirrored by the dangers.

– Rick Anderson, MLIS

Anderson warned that while preprints accelerate dissemination of results by bypassing the peer-review process, this increases the risk of faulty or erroneous results in the published record. However, he argued that preprints could also accelerate the filtering of bad data from the published record as preprints invite the entire research community to review work within hours of posting. These studies can be quickly critiqued by a wide audience and quickly removed if deemed not credible. For example, Cortegiani et al identified dozens of COVID-related papers retracted from preprint servers. Anderson proposes that organizations running preprint servers adopt a policy of actual retraction when posted articles are found to
be fraudulent or fundamentally unsound rather than resorting to a simple banner warning. “I think if preprint servers would genuinely retract—which is to say flag and remove—fraudulent and fundamentally unsound science, it would go a long way towards helping to ameliorate the kinds of public health dangers that we’re seeing right now.” He continued, “It’s so important to get the science out there quickly and publicly, but on the other hand, there’s so much danger in putting bad science out quickly and publicly. All of the benefits are exactly mirrored by the dangers.”

“Preprint servers are a sword that cuts both ways,” he warned. “They are both a benefit and a danger to the public. They are both a benefit and a danger to pharma.”

Anderson also warned of predatory journals, such as the Journal of Health Economics and Outcomes Research or the British Journal of Medical and Health Research. These predatory journals and dozens of others are included in both the Beall’s List of Potential Predatory Journals and Publishers and Stop Predatory Journals. In addition to being open access, these journals are invariably funded by article processing charges. According to Anderson, as long as a manuscript is accompanied by an article processing charge, these predatory journals will likely publish it as peer-reviewed science.

Anderson reiterated that by no means are all open access journals predatory. “There are people in the scholarly community who assume that anytime they’re asked to pay an article processing charge, that means it’s a predatory journal, which is completely false.” He continued, “Predatory journals came into existence exactly as a result of the article processing charge model, not as the result of open access generally.”

“The fundamental problem with these journals is not that they’re low quality; it’s that they’re misrepresenting what they do, defrauding authors and readers alike.”

Open Access
Even traditional journals are evolving to facilitate broader access to research findings by expanding open access to many publications. The term “open access” encompasses a wide mix of publishing models. All of these models provide broad access to published scholarly literature made freely available on the internet where users may read, download, copy, print, or search articles (although not necessarily for unrestricted reuse)—using them for any other lawful purpose, without financial, legal, or technical barriers. The copyright holder (usually the author) must consent in advance to let users “copy, use, distribute, transmit, and display the work publicly and to make and distribute derivative works, in any digital medium for any responsible purpose, subject to proper attribution of authorship.”

These models differ by where and when material is released, who bears the publication cost, and who retains copyright. The 2 most common open access models—gold and green—differ on every attribute. Table 1 compares 4 open access models.

Benefits of Open Access Models
Johan Rooryck, PhD, Executive Director of cOAlition S, (and Visiting Professor at Leiden University), Leiden, The Netherlands, the organization championing open access publishing models, views timely access to critical research as a key factor in

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**Table 1. Comparison of Open Access Models**

<table>
<thead>
<tr>
<th>Model</th>
<th>Site</th>
<th>Version</th>
<th>Availability</th>
<th>Cost</th>
<th>Copyright</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gold</td>
<td>On publisher’s website (only fully open access or hybrid journals)</td>
<td>Published version of record</td>
<td>No embargo</td>
<td>Typically, subject to $3000-$5000 APC</td>
<td>Author retains copyright under Creative Commons license</td>
</tr>
<tr>
<td>Green</td>
<td>Available on an online repository separate from the publisher’s website and self-archived by author</td>
<td>Accepted pre-typeset version or version of record depending on publisher policy</td>
<td>Embargo period (exclusive rights typically reserved by publisher for 6-12 months)</td>
<td>Free of charge</td>
<td>Author typically transfers copyright to publisher, limiting reuse rights</td>
</tr>
<tr>
<td>Bronze</td>
<td>Available on the publisher’s website</td>
<td>Published version of record</td>
<td>With or without embargo</td>
<td>Free of charge</td>
<td>Author typically transfers copyright to publisher, limiting reuse rights</td>
</tr>
<tr>
<td>Diamond</td>
<td>Community-driven (not publisher-driven)</td>
<td>Published version of record</td>
<td>No embargo</td>
<td>Free of charge</td>
<td>Author retains copyright under Creative Commons license</td>
</tr>
<tr>
<td>Platinum</td>
<td>Available on the publisher’s website</td>
<td>Published version of record</td>
<td>Embargo</td>
<td>Free of charge</td>
<td>Author retains copyright under Creative Commons license</td>
</tr>
</tbody>
</table>

APC indicates article processing charge. From ISMPP whitepaper: A multistakeholder discussion on open access and medical publishing.
expediting development of COVID-19 vaccines and treatments this past year. He views publishing embargoes (the time publishers keep research behind paywalls, limiting free access) as particularly burdensome. “If you have to wait 6 months or 12 months because of embargoes, that research is 6 or 12 months old. Imagine if COVID-19 vaccine research had been subject to a 6- or 12-month embargo,” said Rooryck.

Rooryck thinks timely access to new research would not only benefit researchers, but all stakeholders. It could provide practitioners with the up-to-date clinical data needed to improve treatment choices. “Once you open the Pandora’s box [to allow free access] for COVID-19 [research], why not do it for everything? Why not do it for deadly cancers?”

Wider Collaboration, Participation
Open access publishing models can also facilitate engagement of the scientific community in research initiatives. Citation rates of open access articles have been found to be 18% higher than those behind paywalls, although the extent of this citation advantage continues to be debated.11,12 Open access can facilitate further research, advance collaboration, and prevent duplicated research. And by reducing duplication of existing research, scientific progress accelerates.

Proponents of open access argue that publicly funded research should be available to the public. This is especially true for research participants. A recent survey of US-based study participants found that the overwhelming majority (91%) wanted to be informed of study results; two-thirds indicated that their participation in future trials would be predicated on receiving such feedback.13

And patients have voiced a desire to access research beyond that in which they were a participant. In the United States, nearly 60% of adults search for medical information within a given year, with 25% finding their search impeded by paywalls. Only 2% of these patients who encounter paywalls pay for further access; 83% search elsewhere, while 13% give up their search.14

Rooryck believes that not only could open access help educate patients about their treatment, it could also help ensure their participation in future clinical trials. “The lay public is very often educated enough to make up their own minds on the research that’s out there. We want those citizens to be informed,” said Rooryck. “Most of the time, it’s their tax dollars that are paying for this research. They should be the first to benefit. It’s not just about the researchers, it’s about the general audience as well.”

Recognizing Null, Inconclusive, or Validating Research
Highly selective journals seek to publish impactful, often newsworthy, research. Such selectivity often leads to riveting issues filled with thought-provoking and headline-grabbing research. However, Rooryck argues, there are significant concerns surrounding this approach. “Do you really want to say that the 90% of research that you reject should not be published?” he said. “While it is not necessarily front-page news for The New York Times, it may be good, solid research.”

This “good, solid research” may include null studies, validation studies, or inconclusive studies. These findings that are critical to scientific advancement.

Richard White, PhD, Chief Operating Officer at Oxford PharmaGenesis, sees open access as providing an important venue for these less headline-grabbing studies. “I think there’s tremendous wastage out there when a negative study is just put in a drawer and someone else then gets a grant application funded, does the same study, and that could have been money saved and time saved for everyone.

“We need to go much more into a place where there is collaboration instead of competition, where there is validation instead of prestige—a place that is more tolerant of good research rather than just excellent research,” said Rooryck.

The open access models may also help change the perception of HEOR research as potentially biased or less rigorous. Drummond stressed that building trust in HEOR results is more pressing given that regulatory agencies like the US Food and Drug Association (FDA) and European Medicines Agency (EMA) require less evidence for approval as was required 10 years ago. “You have drugs approved on less mature clinical evidence. Health technology assessments are picking up the consequences (of less preapproval clinical evidence) of the FDA and EMA.” With greater transparency, particularly around real-world evidence, trust in HEOR data and the credibility of the research may improve.

We need to go much more into a place where there is collaboration instead of competition, where there is validation instead of prestige—a place that is more tolerant of good research rather than just excellent research.

– Johan Rooryck, PhD

However, Drummond argued that peer review would be critical to bolstering trust. “The industry is very concerned about their message being believable. Peer review is one kind of verification of that message.” He highlighted 2 ways to build credibility—getting published in a highly regarded, peer-reviewed journal or getting FDA approval. “I think industry wants external verification of their message. They are very well aware that people are suspicious of what industry tells them. Therefore, some kind of external verification, of which peer review is one, is important to them.”

Concerns Surrounding Article Processing Charges
Open access may be the future for Value in Health, according to Drummond. “I think we’d like to publish open access. The main problem is the article processing charges and having the funds to pay those.”

He continued, “I think it’s going to lead to some discrimination between the ‘haves’ and the ‘have-nots’ in terms of who can publish open access.” Drummond notes that there is a good chance industry will pay for open access publication of their industry-funded research. Perhaps not all results, but certainly pay for the key result to be published. However, Drummond notes these open access models may be problematic for patient...
Defining Open Access Principles: cOAlition S and Plan S

cOAlition S launched in late 2018 with the goal of making full and immediate open access a standard reality in scholarly publishing. The coalition currently consists of more than 2 dozen organizations, including national organizations in Europe and South Africa and charitable funders based in the United Kingdom and the United States.

In 2018, cOAlition S released Plan S, 10 publishing principles for open access (see Table 2), providing guidance on article processing charges, copyright, and funders. Plan S also discussed “hybrid” open access journals. The hybrid open access model offers authors a choice either to publish behind a paywall free of charge or to publish open access for a fee.

The Plan S principles have now been endorsed by research funders, including the Wellcome Trust and the Bill & Melinda Gates Foundation. Other notable funders who have or who are developing open access policies include the UK Medical Research Council, the European Commission, the US National Institutes of Health, and the National Science Foundation. Early adopters from the pharmaceutical industry include Shire (now part of Takeda) and Ipsen.

All Plan S funders require that articles be published with an open license, for example Creative Commons BY (CC BY). CC BY is recognized as the most permissive license type in that it allows readers to distribute, adapt, and build upon work, assuming they cite the original author.

Rooyrk emphasized that cOAlition S recognizes that pharmaceutical companies may not want to make their research available through open access. However, he notes that the CC BY license would allow these companies to reuse results and perhaps even profit from them. “We have no problem with pharmaceutical companies using research for commercial purposes.”

Changing Publishing Landscape for HEOR Publications

In addition to changes in how scientific data may be disseminated (open access, preprint servers), the medical publishing landscape is expanding to facilitate the dissemination of HEOR evidence.

The industry is very concerned about their message being believable. Peer review is one kind of verification of that message.

– Michael Drummond, MCom, DPhil

White emphasized the importance of new HEOR journals. As he explained, many influential journals in the past lacked reviewers who were familiar with HEOR methodology. “They weren’t trained, weren’t familiar with it. They couldn’t really review it adequately. Definitely proliferation of HEOR has changed publishing hugely.” However, the growing role of groups such as ICER in informing medical decision making means there is now much stronger interest among mainstream clinical and health policy journals in publishing HEOR studies. Coupled with a greater understanding of HEOR concepts among journal peer reviewers, researchers have a wider choice of potential target journals for HEOR studies than ever before.

With this range of options, White recommends a selective approach to targeting HEOR publications. While specialist health economics journals are appropriate for placing more technical or methods-driven studies, he noted that “for potentially practice-changing research, mainstream clinical journals are more receptive to HEOR studies than they have ever been. The leading HEOR and health policy journals, such as Journal of Managed Care & Specialty Pharmacy and Value in Health, also genuinely reach healthcare decision makers.”

Drummond added that the category of journal (ie, clinical journal, health economics journal, or health policy journal) researchers choose to publish in depends on the character of the paper and its core main message. “My main distinction would be as follows: if you are making a point about a particular treatment or healthcare intervention (eg, an orphan drug), go for a clinical journal; if you are making a point about a particular policy issue (eg, the price of orphan drugs or access to orphan drugs), go for a policy journal; if you are making a methodological point (eg, how to evaluate orphan drugs or how to model treatment effect when the data are limited), go for a health economics journal.”

Conclusion

HEOR researchers face a growing and increasingly varied environment in which to share their findings. Many of the recent...
changes to the medical publishing landscape will help provide more open and timely access to more HEOR research. As the rapid-fire development of COVID-19 vaccines has demonstrated, access to timely scientific data is critically important. And as more stakeholders become involved in decision making, “access to all” may need to encompass more patient-facing plain language summaries of clinical research. As Rooryck emphasized, “Research is not a luxury product. It’s a basic necessity.”

But even as the HEOR publishing landscape continues to evolve, many challenges remain. The most pressing question remains who should pay for this new publishing model—authors, funders, readers, professional associations? And who will pay for effective and careful peer review? Academic libraries lack the subscription budget to provide open access to all. Funders have also seen budgets cut while organizations divert funds to tackle the COVID pandemic. Even if funds were available and funders or researchers were to carry this cost, will this slow the progress of critical research?

While free and timely access to scholarly work is highly laudable, the financing structure must ensure this new publishing environment remains a trustworthy source of the highest quality research.

Resources:


References


By the Numbers: HEOR Publishing Landscape

Section Editor: The ISPOR Student Network
Vasco Miguel Pontinha, Virginia Commonwealth University, Richmond, VA, USA; Srujitha Marupuru, University of Arizona, Tuscan, AZ, USA; Enrique Saldarriaga, University of Washington, Seattle, WA, USA; Camila Felix Fortis, Karolinska Institutet, Solna, Sweden

Word Clouds of the Aims of Top 10 Health Economics and Outcomes Research Journals

Discipline: Health Economics
Top Journals:
1. Value in Health
2. Journal of Health Economics
3. Health Economics
4. PharmacoEconomics

Discipline: Decision Making
Top Journals:
1. Medical Care
2. Social Science and Medicine

Discipline: Health Policy
Top Journals:
1. Health Affairs
2. Milbank Quarterly
3. Quality of Life Research
4. Medical Decision Making

Open Access Does Not Seem to Be Very Prevalent in Health Sciences

<table>
<thead>
<tr>
<th>FIELD</th>
<th>PERCENTAGE OF PEOPLE NOT OPEN-SOURCE PUBLISHING</th>
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<tr>
<td>Agricultural Sciences</td>
<td>79%</td>
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<tr>
<td>Engineering &amp; Technology</td>
<td>73%</td>
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<tr>
<td>Social Sciences</td>
<td>62%</td>
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<tr>
<td>Natural Sciences</td>
<td>61%</td>
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<tr>
<td>Medical Health Sciences</td>
<td>59%</td>
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<tr>
<td>Humanities</td>
<td>50%</td>
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Preprint Is a Controversial Approach That Has Been Growing Recently, Mostly Related to COVID-19

The number of publications covering COVID-19 or SARS-CoV-2 on preprint servers (as of May, 2020)

2355 medRxiv
801 arXiv
587 bioRxiv
346 ChemRxiv
To Preprint or Not to Preprint? An Evolving Landscape for the Dissemination of Health Economics and Outcomes Research

Benjamin G. Cohen, PhD, MPH, Monument Analytics, Baltimore, MD, USA; R. Brett McQueen, PhD, Center for Pharmaceutical Outcomes Research, Department of Clinical Pharmacy, University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences, Aurora, CO, USA, Monument Analytics, Baltimore, MD, USA; and William V. Padula, PhD, Leonard D. Schaeffer Center for Health Policy & Economics, Department of Pharmaceutical & Health Economics, University of Southern California School of Pharmacy, Los Angeles, CA, USA, Monument Analytics, Baltimore, MD, USA

The days of journal subscriptions are all but over. The 21st Century has dawned a renaissance in peer-reviewed journal readership, as researchers contemplate multiple options to publish. One can publish in a traditional journal submission process where readers or institutions pay journal license fees to read or subscribe to the publication. Another option is to publish in open access literature, where the researcher or their sponsor actually pay the journal to make the article openly available to the public. The third, more recent option is to post findings on a "preprint" space so readers can access the content before it has even been peer reviewed. This third option presents a number of noteworthy pros and cons to consider that are particularly important to the health economics and outcomes research (HEOR) community as the demand for timely findings becomes more immediate.

Take the current state of the COVID-19 pandemic. The need to share findings immediately has never been more important, as COVID-19 research findings of the early outbreak in Asia may have benefited billions of susceptible individuals by limiting their exposure to infection in Europe and North America. With few exceptions, the peer review process could not facilitate access to research quickly enough to make such findings accessible as infection spread exponentially. Expedited publishing through preprint media facilitated early access of scientific findings, even if not fully vetted by external peer review.1

Preprints increase the speed of access to science, allowing stakeholders to interpret data sooner for expedited decision making.2 While preprints eschew traditional assurances of scientific rigor, they do present the HEOR community with a belief that it has embraced through value of information: more data are always better, even if those data encapsulate additional uncertainty.

What the HEOR field has not been scrutinized for in the past, however, is related to a worldwide concern over the spread of misinformation, to which preprints are equally susceptible. An overall increase in information can amplify the noise in the public space and result in the spread of misinformation, especially when left open to interpretation by individuals without technical training or experience who would not normally access peer-reviewed journals with HEOR-specific content, for instance. Peer-reviewed journal articles reliably reach audiences with the appropriate technical expertise to process and interpret the methods and results. Ceding control of the information flow allows for a quicker advance of ideas, yet issues arise when findings are misunderstood.

Along with these concerns, there are a number of other pros and cons of preprint access to HEOR studies that may be more apparent as a result of the COVID-19 pandemic. We provide a brief overview of the following pros and cons of studies in preprint in the Table.
Table. Pros and cons of preprint publication of HEOR findings with respect to the peer-review process.

<table>
<thead>
<tr>
<th>Issue</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model Transparency</td>
<td>If open-sourced and in preprint, then economic models are mostly transparent and can give investigators feedback to strengthen model uncertainty as they approach the peer-review process.</td>
<td>If only available in peer-reviewed literature, then there is variability of understanding the economic model based on space constraints, which could impact replicability of study findings.</td>
</tr>
<tr>
<td>Model Advancement</td>
<td>If the economic model is released in preprint and designed to be transparent, then other professionals can manipulate the model with locally relevant or new data.</td>
<td>Updating the model requires good actors and people with the right HEOR skills and abilities to work with these models; originators of economic models may not be appropriately credited as updates are made with locally relevant or new data.</td>
</tr>
<tr>
<td>Reach</td>
<td>Wider audiences may not have access to journal licenses, particularly in low- and middle-income countries.</td>
<td>Wider audiences may not have the appropriate HEOR background to interpret findings accurately.</td>
</tr>
<tr>
<td>Timeliness</td>
<td>Preprint media present fewer barriers to dissemination when time is precious and gets results into the hands of decision makers.</td>
<td>Economic models could have unchecked flaws that might lead to avoidable, negative consequences such as undeserved coverage, wasted spending, or uninformed policies.</td>
</tr>
<tr>
<td>Misinformation</td>
<td>Preprints provide earlier access to the most up-to-date information.</td>
<td>Publishing in a peer-reviewed journal ensures reaching an audience with the appropriate expertise; lay audiences could easily misconstrue findings that lead to negative consequences.</td>
</tr>
<tr>
<td>Public Education About Economic Models</td>
<td>Publicly available models accelerate the flow of information on a topic that could lead to more topical HEOR productivity in advance of the long road to peer review.</td>
<td>Currently, the public might not have the ability to understand the nuances of the findings.</td>
</tr>
<tr>
<td>Costs for Accessibility</td>
<td>Accessible to anybody with internet and does not usually require a gatekeeper (eg, publisher).</td>
<td>Normally, somebody needs to pay for access; allows for the ability to pay for information to enter the public arena, even if it might not belong there.</td>
</tr>
</tbody>
</table>

**HEOR** indicates health economics and outcomes research

**Model Transparency and Advancement**

Preprint articles and open-sourced economic models allow for increased transparency and scrutiny from a wider variety of readers. Authors are also able to receive feedback to strengthen the economic model results as they approach the peer review process. Furthermore, printing models and other economic findings only in peer-reviewed literature creates a variability in understanding due to space constraints. Despite the ability to publish appendices and additional information online, it is challenging to include the complete description of a model's functionality in a journal article. In turn, this limits the interpretation, advancement, and replicability of the model.

Admittedly, publishing through peer review shows comprehension of the theory and application of HEOR methods. HEOR experts conduct highly technical research that requires significant training to understand and appreciate. Increased transparency can allow other HEOR experts to validate and advance available literature, but that does not necessitate preprints.

Publicly available and transparent economic models can be manipulated by HEOR experts to include locally relevant or new data. Users can then generate more individualized and up-to-date results. Advancements in this manner, nevertheless, require the updates to be made by good actors and users who have the skills and abilities to work with the models. Inappropriate use, intentional or not, could lead to spurious, misinterpreted, or misapplied results. Therefore, peer-reviewed journals may learn from health technology assessment agencies (eg, ICER, IVI, NICE, etc) about their experiences with open source and/or model sharing programs.

**Looking at Reach and Timeliness**

While journals are less likely to publish articles that have already reached a broad audience through preprint servers, preprints can reach a larger audience that may not have journal access—not just laymen, but HEOR experts in low- and middle-income countries with limited institutional subscriptions. However, expanding an article's reach alone does not expand the pool of individuals who can interpret the results. It is undoubtedly important for HEOR to reach clinicians, health system leadership, and decision makers. Yet, simply increasing the publication's visibility does not translate into more decision makers accessing a study, such as in preprint form. If anything, decision makers would likely embrace the peer-review process so that their own decisions are based on greater certainty. Assurances should be taken to help individuals without HEOR expertise to understand the findings in the appropriate context.

Preprints also provide a timeline advantage for both authors and audiences through quicker access to the public domain. When done appropriately, the expedited timeline and publicly available information allows for greater scientific advancement.
The peer-review process, while slower, provides readers with the confidence that the information they are reading is truly science. Without peer review, readers are left to determine the quality of the work on their own. This is unlikely to be a problem for experts in HEOR but is more complicated when applied to the wider readership.

Public Education About Economic Models and the Cost of Accessibility

Lay audiences likely do not have the necessary expertise to understand complicated results produced by HEOR studies (eg, cost-effectiveness analysis or econometric modeling). Allowing for these economic models to reach wider audiences could spur interest in HEOR, but the public currently may not have the ability to understand the nuances of the work.

Preprints are usually accessible to anybody with an internet connection, thereby bypassing the delays and charges associated with the existing peer-review process. While this may seem like a win-win, the journals that act as gatekeepers to high-quality HEOR studies could lose financial support in the long run as preprint popularity increases. Placing peer-reviewed journals in dire financial straits could be a consequence to HEOR that is not worth the risk, considering a dissemination system without checks and balances could flood the HEOR mainstream with misinformation.

Conclusion

The demand for HEOR evidence on a shorter timeline from study conception to reporting results is growing internationally. When acute health consequences such as the COVID-19 pandemic presents a small window of opportunity to share information in order to save lives, preprints offer an alternative to the long haul of peer-review processing. This eagerness to publish results quickly aligns with the attitude of HEOR experts to contribute to improving healthcare’s accessibility and quality at lower costs. That said, more immediate information does not always equal better quality information. HEOR dissemination in preprint comes with a clear tradeoff that it is not yet vetted.

As a result, some preprints simply amplify the noise that would not pass through the peer-review process. The potential for increased misinformation and confusion cannot be understated in the current environment. Preprints have, and can, provide value to the field through increased visibility and speed, but one must be cognizant of the challenges associated with preprints when both publishing and reading these articles.

References

Conducting a gold-standard systematic review is a laborious and time-consuming process.

The authors argue that this process can be improved by rethinking some of the fundamental assumptions about the goals and products of systematic evidence reviews.

How can action-guiding evidence be gathered with sufficient speed, reliability, depth, and flexibility?

It is easy to say that decisions about planning and design for clinical research should be informed by a comprehensive understanding of the existing evidence. Indeed, in the era of evidence-based medicine, this prescription should seem axiomatic. Whether we are referring to clinical development teams in the pharmaceutical industry planning a translational research program, research funding organizations deciding which project applications to fund, or academic investigators planning and designing their next study, the more that each of these groups understand about what has already been done, what worked well (or did not) in the past, and where the highest value opportunities are, the better.

But while it is easy to say that these kinds of decisions should be based on a comprehensive understanding of the evidence, it is far harder to say exactly how this should be accomplished. In much of the trial methodology literature, for example, it is suggested that these decision makers should refer to the latest, relevant systematic review.1,2 Or if there is no such review, then they should first conduct a systematic review to establish (a) that their proposed line of research has not already been done by someone else, and (b) that their research design decisions are aligned with the best standards and practices.

Unfortunately, conducting a gold-standard systematic review is a laborious and time-consuming process, often taking teams of experts more than 12 months to complete.3 As informative and valuable as this exercise might be, some research and development activities simply cannot be delayed a year or more. Or even if there is already a published systematic review to draw on, given the time it took the authors of that review to complete the work and get it through the peer-review and publication process, the underlying data are likely to be a year or more out-of-date.

Thus, we arrive at one of the paradoxes of evidence-based decision making in clinical research and development: there is widespread agreement that better research will result from first having a comprehensive understanding of the existing evidence in hand. But because time is precious and decisions about what studies to conduct and how to conduct them may not be able to wait a year, a comprehensive, up-to-date understanding is often out of reach.

However, in what follows, we argue that this paradox can be resolved by rethinking some of the fundamental assumptions about the goals and products of systematic evidence reviews.

The Silver Standards of Evidence Synthesis

But before describing our more radical solution, we should first acknowledge that there are a number of alternatives to the gold-standard systematic review.4 Rapid reviews and scoping reviews are 2 methodologies that aim to strike a more time-sensitive balance between the thoroughness of an evidence assessment and gaining sufficient insight to act. The rapid review, for example, will often use a similar search methodology to a full systematic review but will not go as deep into the data extraction or evidence-quality assessment. Or a scoping review may abandon an evidence assessment entirely, and instead focuses solely on providing insight about the size and breadth of the existing evidence base. Both of these approaches can be completed much more quickly than a full systematic review, sometimes taking only days or weeks rather than months. If a primary goal of the evidence review is something like a gap analysis (ie, identifying important questions or clinical needs that have not yet been addressed by any existing studies) then these leaner approaches may be viable alternatives.

It is also worth noting that there are data and analytics companies that aggregate and track data on clinical research programs, or consulting firms that will conduct a complete systematic review and produce recommendations about optimal next steps. For decision makers that have
the resources, these companies may be an ideal solution. Data providers may be able to offer all the evidence needed to inform next steps straight “off the shelf,” so to speak. Although consultant firms often still conduct systematic reviews the slow, traditional way, with enough lead time they may provide the richness and depth of analysis needed without requiring their clients to have “personally” expended the time.

However, there are some devils in the details of even these “silver-standard” evidence synthesis options. For example, in the case of purchasing data from a provider, the provenance of the data, as well as the various operations or transformations that have been performed on the data, are not necessarily transparent. This can make it impossible to verify the reliability of the data or any insights derived therefrom. Indeed, this is one of the major reasons for systematic review reporting standards: By documenting every step of the review process, the consumer of the systematic review can have greater confidence that any decisions flowing from it are grounded in a scientifically valid and reproducible process.

But an even more fundamental challenge for all of these evidence synthesis options is the fact that many of the key terms needed to classify and make sense of biomedical research data are fuzzy, change over time, or are disputed by the experts in the field. For example, even a question as seemingly basic as “What specific disease was being studied in a given clinical trial?” may not have one, clear answer. This could be because the way diseases are classified has changed over time. It could be because there are multiple existing biomedical ontologies, and they do not all perfectly overlap. It could also be because the “correct” (or most useful) way to classify the disease of interest in a study depends upon the needs of the decision maker.

This problem of classification is by no means limited to just disease terms. Classifications for drug mechanisms of action, intervention types, population characteristics, inclusion/exclusion criteria, and outcomes are also often fuzzy, disputed, subjective, or context-sensitive. It is therefore necessary for the evidence reviewers to commit to some taxonomy or ontology for these classifiers. For the formal evidence review methodologies, the reviewers are supposed to prespecify the taxonomy/ontology they will use and publish a codebook along with the results that allows the reader to understand their judgment process. Data-providing companies would also ideally make their chosen ontologies and judgment processes explicit for the same reason.

Yet because the problem here is not merely due to multiple classification ontologies but rather stems from fundamental uncertainties in biomedicine (ie, our best understanding is constantly evolving as we learn more), then merely making the ontology and the supporting judgments explicit still does not quite solve it. To truly solve the problem we need to give decision makers a way to quickly aggregate and view relevant evidence with a taxonomy that is suited to their purpose. In other words, the taxonomy of an evidence review also needs to be flexible, so that different “consumers” of the evidence can apply different sets of concepts or classification schemes. Traditional systematic review methods provide all the depth and flexibility needed to do this (because each project can construct its own taxonomy and codebook to suit its purpose), but they are simply too slow. Leaner review methods have speed and flexibility, but may lack the depth needed to optimally inform next steps. The existing “off-the-shelf” data providers have the speed and (often) the depth required, but not the flexibility.

Towards a New Metascience Solution

So can we have it all? Is there a way to give decision makers the speed, depth, and flexibility to evaluate the existing evidence and make the most informed decision possible about what to do next? We believe that the answer to this question is yes but it requires some significant shifts in how we think about the goals and products of an evidence review.

Figure 1. Screenshot of user interface for an evidence review of all nonpharmacological trials in Alzheimer’s disease and related dementias (ADRD).

The main body of the application shows summary metrics (eg, the total number of trials, participants, interventions, and outcome types, etc) followed by a series of charts that describe distributions or relationships between trial parameters. The menu panel on the left side of the page provides filters for all the major fields in the dataset, allowing the user to dynamically exclude trials that are not of interest, and then immediately update the rest of charts and analytics. This user interface also allows the authors to include commentary (as shown in the bottom right) to provide interpretation and context that may not be apparent from the data visualizations alone.
The first shift is to think of an evidence review as a continuous process that should function more like a “living application” that decision makers can interact with and monitor on a regular basis, rather than a one-off, linear project whose end-state will be a static publication. For example, we are currently working on an evidence synthesis project whose goal is to inform pilot trials with promising, nonpharmacological interventions that can improve the quality of care for people with Alzheimer’s disease and related dementias (ADRD). To help achieve this goal, we have created an automated search and data extraction algorithm that can regularly query ClinicalTrials.gov for all registered clinical trials and outcomes studies involving nonpharmacological interventions, import these data into a relational database, and then represent the data with a dynamic, visual user interface like the one shown in Figure 1. This approach offers the necessary speed to provide meaningful evidence on the evidence in real-time, without having to wait weeks or months to get an understanding of the scientific landscape before making a decision.

A second shift is to recognize that all the data transformation (eg, cleaning, normalization, and classification) processes in an evidence review should be transparent. For published systematic reviews, the readers typically only get to see the PRISMA flow chart, the summary results (presented in static tables), and perhaps a supplemental spreadsheet with the underlying data in its final state. But the vast majority of judgments that transformed the raw data (which often started as just a list of potentially relevant PubMed/Embase/ClinicalTrials.gov IDs) into a spreadsheet full of valuable classifications remains opaque. Commercial providers are not typically better here since they often do not disclose sufficient details about the processes and algorithms they use. While there may be good business reasons for this opacity, the lack of transparency is anathema to scientific integrity and poses a threat to trust and confidence in the quality of their data.

A third shift, closely related to the second, is to think of the data analysis and presentation as dynamic and evolving. Essentially, we believe that evidence reviews should always be considered ongoing works-in-progress. The data and their analysis will be changing and updating over time, and this is as it should be, given that the scientific community’s understanding is also growing and changing. For example, Figure 2 shows a detailed view of the data-filtering menu from the same ADRD evidence-review user interface mentioned above. This menu allows the user to select/deselect particular types of outcomes and include/exclude those trial records from the analysis. But this particular list of outcome terms, which is the result of a semisupervised, natural language-processing algorithm, is not fixed. As we alter our taxonomy and revise or improve the algorithms over time, this menu and the results of the analysis will change. But since our source data, with their provenance and history of changes, can all be saved in the underlying database, this evolution in how the evidence is processed and interpreted will no longer be problematic. As the science and evidence evolve, so too should our analysis.

In fact, we would argue that the ability to reclassify data and track the history of such changes represents a profound advance in science (or meta-science to be more precise). Indeed, we see this as a key step for overcoming the problems with shifting, inconsistent, or disputed ontologies. Two experts may want to classify the same data in different ways and have this reflected in the evidence review, and like everything else in the framework, it should be considered an evolving work-in-progress. For some purposes, this “flat” taxonomy of outcomes may be sufficiently informative. For other purposes, an entirely different set of terms or groupings of outcomes may be more useful. The framework we envision is designed with this flexibility in mind, giving different users/teams the ability to code the data in different ways and have this reflected in the user interface.

So can we have it all? Is there a way to give decision makers the speed, depth, and flexibility to evaluate the existing evidence and make the most informed decision possible about what to do next?

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Conclusion

In sum, the value of evidence-based decision making to guide future research is uncontroversial. Everyone largely agrees that the more we can marshal the “evidence on the evidence,” the more likely we are to make good decisions about next steps and prevent wasteful research. The longstanding challenge...
has thus been more of a technical one—how can we gather the evidence on the evidence with sufficient speed, reliability, depth, and flexibility? We have argued that these technical challenges can be solved once we stop thinking of evidence synthesis as a linear process that should be done before we act, but rather as an ongoing process of building “living” software applications that give us real-time visibility over the scientific landscape.

References


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The desire, opportunity, and willingness to increase access to potentially life-saving cancer treatments has mounted in recent years. As the landscape of drug development changes, the criteria for evaluating uncertainty must also change. Some believe the Cancer Drugs Fund (CDF) framework should be evaluated to ensure it can operate to its full potential. In this article, we explore potential changes to both the processes and infrastructure of managed access in England as a means of optimizing access for patients.

What Is the Cancer Drugs Fund?
The government of the United Kingdom established the CDF in 2010 as a mechanism to pay for cancer drugs not yet approved for use by the National Institute for Health and Care Excellence (NICE). The CDF is a key component of managed access in England, giving patients access to promising treatments at lower prices earlier while further data are collected to resolve uncertainties specified by NICE. At its core, the principles are quite simple; following a first assessment, NICE now has an option to make an interim funding decision, a “yes on the CDF,” enabling reappraisal at the end of the data collection period. If the treatment is found to be a cost-effective use of resources, it may be then approved for use via routine commissioning, accompanied by a mandatory funding directive. These routes of commissioning are illustrated in Figure 1. In cases where there is plausible potential for cost-effectiveness but substantial uncertainty, a managed access agreement and further data collection may be agreed upon with the CDF.

All signs trend towards there being greater reliance on managed access in the coming years. Advances in personalized medicine development bring the promise of important clinical benefits. With these developments, however, come unprecedented levels of uncertainty in the evidence base upon which reimbursement decisions are to be made. Pairing this with increased budgetary pressure means new complexity around how to appropriately manage access to new treatments is unavoidable. The advent of these new technologies is therefore heavily reliant on the willingness of payers to adapt to accommodate them.

The Taxonomy of Uncertainty
Before considering how the current system could be reformed, it is worth commenting on what we mean by “addressing uncertainty.” In the context of NICE, mechanisms to address

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**Figure 1. Schematic of routes to commissioning in the National Health Service in England for new medicines.**

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Health Technology Appraisal

- **?** Plausible potential for cost-effectiveness but uncertainty remains
  - Managed access agreement
- **✓** Clinically and cost-effective
  - Routine commissioning
- **✗** Not recommended
  - Not funded
uncertainty can be categorized under 2 broad headings: (1) effectiveness-based solutions and (2) cost-based solutions.

In its simplest form, in cases where overall survival (a key outcome in oncology) may be immature, longer follow-up from an existing clinical study may increase confidence in modeled long-term estimates. In theory, overall survival data can be collected while the treatment is made available through the CDF, and then used in a reevaluation of cost-effectiveness by decision makers.

If the key area of clinical uncertainty can be resolved by the maturation of existing clinical studies, the current arrangements can continue to be effective. Frequently, however, comparator efficacy is identified as a primary source of uncertainty, but few data collection agreements seek to obtain new comparative evidence. Expanding the options for data collection should increase the likelihood that, on reappraisal, key uncertainties identified during the initial appraisal can be appropriately addressed. Figure 2 breaks down the key decision-making criteria considered when evaluating whether a treatment would be eligible for approval via the CDF. In all cases, an a priori assumption that uncertainty can be resolved by further data collection is required.

The other side of the equation is cost, namely drug acquisition cost. Where the evidence base is uncertain, manufacturers may decide to trade off uncertainty for each specific indication while the treatment is available through the CDF. Upon reevaluation such flexibility will cease.

Data-Based Solutions: Is the Systematic Anti-Cancer Therapy Dataset Fit for Purpose?
The Systematic Anti-Cancer Therapy dataset (SACT) is mandated as part of the Health and Social Care Information Standards that collects information on using systemic anticancer therapies across all National Health Service England Trusts. In all cases, when a treatment is approved for use via the CDF, data collection via SACT is undertaken in a formal data collection agreement. As is shown in the Table, the list of therapies and disease indications that are subject to active SACT data collection in England is substantial. Some of these treatments will be shown to be cost-effective and become available for routine commissioning upon reappraisal and some will not. While access to these data following a predefined CDF data collection period can help decision makers understand how a drug may be used in practice, SACT has several shortcomings as a primary evidence source. First, complete data collection is limited to few outcomes—primarily overall survival, time-on-treatment, and subsequent treatment. Data on health-related quality of life or even progression-free survival do not often lend themselves to collection in the “real-world” due to differences in reporting and monitoring practices. The development of more diverse and accessible data systems may allow manufacturers and NICE to address a broader range of uncertainties. Second, the burden of data collection in the current system falls to the National Health Service. With the number of treatments approved via the CDF only set to increase, there should be real concerns about this ever-growing administrative burden.

Alternative data collection models, such as those described by Grieve, et al., propose using “only in research” recommendations, encouraging the commissioning of additional, randomized controlled trials to establish relative drug efficacy without the need for observational data and application of advanced statistical methods to form comparisons. Although randomized controlled trials are considered the gold standard for establishing the safety and efficacy of a drug, they do not determine how the drug will perform in real-life clinical practice compared to the standard of care in the National Health Service. This is the main question that NICE is seeking to answer. Moreover, from an ethical perspective, there are conditions where assigning patients to the control arm of a study where they might receive suboptimal treatment should be discouraged.

A middle ground between new randomized controlled trials and routine data collection via the SACT could be a subsidized registry system whereby data collection and access are funded, at least in part, by manufacturers and coordinated in collaboration with methods experts at NICE. The goal of such a system would be to address a broader range of uncertainties, improve clarity in how the data collection will be used to inform reappraisal, and crucially, help ameliorate the administrative burden currently borne by the National Health Service.

Figure 2. Cancer Drugs Fund eligibility flow diagram.

<table>
<thead>
<tr>
<th>Proceed across if the answer to each question is yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is the model structurally robust for decision making?</td>
</tr>
<tr>
<td>2. Does the drug have the plausible potential to be cost-effective?</td>
</tr>
<tr>
<td>3. Could further data collection reduce uncertainty?</td>
</tr>
<tr>
<td>4. Will ongoing studies provide useful data?</td>
</tr>
<tr>
<td>5. Is Cancer Drugs Fund data collection via Systematic Anti-Cancer Therapy relevant and feasible?</td>
</tr>
</tbody>
</table>

Consider entry into the Cancer Drugs Fund

Define the nature and level of clinical uncertainty. Indicate the research question, analyses required, and number of patients in NHS in England needed to collect this data.

NHS indicates National Health Service.
Cost-Based Solutions: Buying Out Uncertainty

Improvements in data quantity and quality will take time and decisions will always need to be made in the context of imperfect information. Indeed, in some cases uncertainty may be unresolvable because the time required to generate sufficient evidence may be too long. It is here that an expansion in the approach to drug pricing could be valuable.

One option could be to allow companies to offer different prices across different indications. This would mean that for each indication considered, the manufacturer would have the ability to apply a different price based on the value offered by the treatment in a given indication and the uncertainty that remains in the evidence base.

While some progress towards commercial flexibility has been made in the National Health Service Commercial Framework for Medicines, this is focused towards medicines at or below the lower end of NICE’s willingness-to-pay range. The reality is that drugs with the potential to be highly effective are struggling to gain access due to uncertainty in the evidence base, and these are unlikely to provide sufficient return on investment at or below the lower end of the willingness-to-pay range. Changes to the system, whether the implementation of new or expansion of current commercial options, must ensure that the implementation of such arrangements minimizes the administrative burden on National Health Service England and front-line staff. In time, the Commercial Framework should pay for itself through rebate systems, but participation must be encouraged.

Looking Ahead

As the drug development pathway changes so should both the CDF and the wider health technology assessment landscape to accommodate those changes and to keep pace with evolving patient needs.

Table. List of drugs in the Cancer Drugs Fund that are subject to an active Systematic Anti-Cancer Therapy data collection.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daratumumab</td>
<td>Janssen</td>
<td>Multiple myeloma (relapsed/refractory, +3L) B-cell receptor pathway inhibitors</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>AbbVie</td>
<td>Chronic Lymphomatic Leukemia (17p del /TP53 mut—unsuitable/failed B-cell receptor pathway inhibitors or no 17p del /TP53 mut failed chemoimmunotherapy and B-cell receptor pathway inhibitors</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>Roche</td>
<td>Urothelial—advanced (1L—unsuitable for cisplatin therapy)</td>
</tr>
<tr>
<td>Nivolumab with ipilimumab</td>
<td>Bristol Myers Squibb</td>
<td>Renal cell carcinoma</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Merck Sharp &amp; Dohme</td>
<td>Adjuvant treatment of melanoma with high risk of recurrence</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>AstraZeneca</td>
<td>Non-small cell lung cancer</td>
</tr>
<tr>
<td>Palbociclib + fulvestrant</td>
<td>Pfizer</td>
<td>Metastatic, hormone-receptor positive, human epidermal growth factor receptor 2-negative</td>
</tr>
<tr>
<td>Cemiplimab</td>
<td>Sanofi</td>
<td>Cutaneous squamous cell carcinoma</td>
</tr>
<tr>
<td>Rucaparib</td>
<td>Clovis Oncology</td>
<td>Ovarian, fallopian tube and peritoneal cancer</td>
</tr>
<tr>
<td>Daratumumab with bortezomib</td>
<td>Janssen</td>
<td>Multiple myeloma squamous cell carcinoma</td>
</tr>
<tr>
<td>Axicabtagene cileoleucel</td>
<td>Gilead/Kite</td>
<td>Diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies</td>
</tr>
<tr>
<td>Isatuximab with pomalidomide &amp; dexamethasone</td>
<td>Sanofi</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Merck Sharp &amp; Dohme</td>
<td>Relapsed or refractory classical Hodgkin lymphoma</td>
</tr>
<tr>
<td>Venetoclax (with obinutuzumab)</td>
<td>Sanofi</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Tisagenlecleucel</td>
<td>Novartis</td>
<td>Diffuse large B-cell lymphoma</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>Pfizer</td>
<td>ROS1-positive advanced non-small cell lung cancer (any line)</td>
</tr>
<tr>
<td>Tisagenlecleucel</td>
<td>Novartis</td>
<td>Relapsed or refractory B-cell acute lymphoblastic leukemia in people aged up to 25 years</td>
</tr>
<tr>
<td>Larotrectinib</td>
<td>Bayer</td>
<td>Neurotrophic tyrosine receptor kinase fusion-positive solid tumors</td>
</tr>
<tr>
<td>Avelumab with axitinib</td>
<td>Merck and Pfizer</td>
<td>Untreated advanced renal cell carcinoma</td>
</tr>
<tr>
<td>Olaparib</td>
<td>AstraZeneca</td>
<td>Maintenance treatment of newly diagnosed breast cancer risk assessment-mutated advanced ovarian, fallopian tube, or peritoneal cancer, after response to first-line platinum-based chemotherapy</td>
</tr>
<tr>
<td>Niraparib</td>
<td>GlaxoSmithKline</td>
<td>Ovarian, fallopian tube, and primary peritoneal cancer</td>
</tr>
<tr>
<td>Entrectinib</td>
<td>Roche</td>
<td>Neurotropic tyrosine receptor kinase fusion-positive solid tumors</td>
</tr>
</tbody>
</table>

Notes: Accurate as of January 2021; SACT Homepage (chemodataset.nhs.uk).
The COVID-19 crisis has highlighted the urgent need to invest in National Health Service data to inform population health. Introducing system-level improvement in real-world data collection, management, and access could contribute to resolving clinical uncertainty in specific populations or societal welfare as a whole. If manufacturers, NICE, and the National Health System can jointly shoulder both the initiative and cost of reform, more opportunities will be unlocked for patients. Introducing formal flexibility for true risk-sharing pricing schemes would allow manufacturers to trade off the uncertainty in the clinical evidence. Doing so would allow NICE to remain innovators in health technology assessment decision making, help establish an appropriate process for which manufacturers and National Health Service England can share risk, while securing continued access to the most promising treatments for patients in England and Wales. Through joint investment in evidence generation infrastructure, research to refine methods of analysis and a willingness to explore alternative approaches to pricing, the capacity for informed decision making greatly increases. While having complex arrangements in place for every treatment assessed is clearly not feasible, more needs to be done to find pragmatic solutions without compromising the timeliness of patients’ access to treatment.

References
Novel Elements of the Value Flower: Fake or Truly Novel?

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At ISPOR's 22nd Annual European Congress in Copenhagen, Denmark, an issue panel convened to discuss the novel elements of value proposed by ISPOR's Special Task Force on US Value Assessment Frameworks.1, 2 The panelists debated whether the elements were truly novel and relevant for decision making, or whether this news was “fake.” They further discussed how to incorporate these novel elements into cost-effectiveness analyses. Whereas the task force had focused on the US setting, the panelists considered their relevance also in other health technology assessment (HTA) settings.

Sarah Goring:
The Value Flower and Elements of Value

The task force introduced the “value flower” (Figure 1) as a type of augmented cost-effectiveness analysis.2 The 12 petals represent elements of value: 2 elements (costs and quality-adjusted life-years [QALYs] gained) represent existing cornerstones of value in health; 2 elements (adherence and productivity) are relatively common, yet inconsistently incorporated into cost-effectiveness analysis; and the remaining 8 are considered potentially novel.

Several of the more novel elements of value relate to uncertainty. The value of hope captures differences in patients’ risk tolerance: whereas some may value a treatment with high variability in outcomes (with the hope that they may be among the few who respond very well), others may prefer a treatment with less variability around expected outcomes. The value of knowing pertains to the pairing of a new treatment plus a new test that can accurately predict who will respond; it captures the additional value stemming from that knowledge. Real option value is more forward-looking. In therapeutic areas on the brink of a major

As moderator, Sarah Goring introduces the “value flower.” Lou Garrison reflects on the ISPOR Special Task Force work, provides context for its genesis and recommendations for future work. Jeroen Jansen presents methodological detail for 2 elements of value related to uncertainty and risk preference and argues that future research to understand its relevance and credibility may be worthwhile. Andrew Briggs provides a critique of the novel elements of value, arguing in favor of the cost-per-QALY metric for capturing value.

Although “fake” and “novel” are hardly antonyms, it can be argued that they are neither novel or necessary.

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The authors recommend further methods development and testing of alternative approaches that build on a cost-per-QALYs metric.

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Figure 1. The Value Flower.
shift in treatment efficacy (think of the era slightly before curative drugs for hepatitis C), patients and payers may be willing to pay more for a life-extending therapy to enable the possibility of receiving the curative medicine when it becomes available. Alternatively, they may forego inferior treatments—at some risk—to wait for the curative treatment.

Insurance value also reflects the benefit of reducing uncertainty through access to a health plan's benefit package. It captures the value to healthy individuals of being protected from the physical and financial burden of a particular illness due to the availability of a new therapy/technology. This is particularly relevant for severe diseases, of which healthy individuals tend to be more fearful. In this way, the severity of disease value element is related. Research shows that incremental gains in utilities of say, 0.1, may be considered more valuable when applied to more severe disease; however, this type of weighting is not captured in traditional cost-effectiveness analysis.²

Equity in healthcare is of paramount value to society yet tends not to be explicitly captured in traditional cost-per-QALY metrics. Several attempts to formally quantify and evaluate impacts of health interventions on equity in an HTA setting have already been made, and the task force identified this as an important area for future work.³

The last 2 value elements are types of system-level “externalities”: fear of contagion (germane to the current pandemic) and scientific spillovers (research and development activities can add broadly to our collective knowledge).

Lou Garrison: Reflections on the ISPOR Special Task Force on US Value Frameworks

Beginning around 2014 and in the short span of a couple of years, 5 “value frameworks” for new medicines were launched or promulgated in the United States. These frameworks seemed to be creating some confusion, so ISPOR formed a Special Task Force in 2016 to review them from a health economics perspective. Peter Neumann, Dick Wilke, and Lou Garrison were co leaders of this group of 10 distinguished US and ex-US economists—supported with feedback from a multidisciplinary review panel. The task force published its report in February 2018 and published an article in November 2019 with reflections on the task force effort, making observations and a key recommendation.⁴

The key takeaway was that this ISPOR Special Task Force “recommended further methods development and testing of alternative approaches that build on a cost-per-QALY metric, including augmented cost-effectiveness analysis and multicriteria decision analysis in support of deliberative processes.” The augmented cost-effectiveness analysis value flower identified some “potential novel elements of value,” but they were not intended as an exhaustive list and/or a definitive list of what is “novel.” All of these elements were identified in prior research. Indeed, the task force endorsed the conventional cost-per-QALY metric as a foundational concept to be built upon and augmented. A key point from a US perspective is that this endorsement goes against legal prohibitions against the use of the QALY in the US Medicare program.

The task force also argued that the cost-per-QALY metric has limitations in theory and in practice that need to be addressed—hence, the need for more work on augmented cost-effectiveness analysis and multicriteria decision analysis as 2 alternative approaches. The task force conceived of value from an economic perspective defined as what individuals would be willing to pay or to forego (“opportunity cost”) in order to have insurance coverage for more healthcare. This is in contrast with “clinical value” in the regulatory sense of the net balance of the benefits of a new medicine versus its risks. Clearly, clinical value is key to “health gain”—one of the 2 key drivers of value in innovative medicines, with the other being “net cost,” which is also affected by clinical value. The QALY measures health gain in terms of length of life and quality of life. In theory, some might argue the QALY is fully comprehensive if health-related quality of life is defined as “everything that is not length of life.” In practice, our estimation of health state utility, via, for example, the EQ-5D or time trade-off technique cannot—given the cognitive limitations of humans—consider everything that matters. Hence, the important US Second Panel of Cost-Effectiveness argues that some elements, such as productivity, are best monetized in the numerator of the cost-effectiveness ratio rather than in the denominator.⁵ The same rationale for monetization in augmented cost-effectiveness analysis may apply to the novel elements to include in estimating the expected net monetary benefit of specific interventions.

In characterizing the 5 frameworks, the task force also emphasized “decision context” and perspective. Figure 2 illustrates a “cascade” of decision contexts and recent value frameworks: a cascade from the plan level to the patient level.
Two additional components of value related to risk preferences have been labeled “insurance value” and “value of hope” in the value flower. Unfortunately, these labels may lead to a misunderstanding of the concepts and downright rejection of their relevance (eg, “studying the value of insurance is only relevant for the United States where there is no universal coverage”; “incorporating hope is the antithesis of rational cost-effectiveness analysis-based decision making”). However, the formal integration of the value that a new health technology provides by affecting the uncertainty that individuals face regarding health outcomes in the cost-effectiveness analysis framework is useful to consider.

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Availability of an efficacious (and safe) intervention for a certain disease does not only provide value to patients, but also provides value to healthy individuals at risk for that disease. An efficacious intervention provides some degree of protection against the physical risk of the disease. For example, the vaccines that are now available for SARS-COV-2 mean that we all have less to fear from it, even though not all of us would develop COVID-19. In addition, an efficacious
intervention converts an uninsurable physical risk (getting sick) into a financial risk, which can be mitigated by health insurance.

Conventional value of a new intervention relative to standard of care from the perspective of a healthy individual at risk of the disease can be calculated as the marginal value to sick patients multiplied by the probability of getting sick.\(^{10,11}\) We account for risk by scaling the ex post (that is, after the health disorder is realized) value of the intervention by the probability of falling ill. This simple approach implies that individuals are risk neutral. If we want to incorporate risk aversion, we need to adjust the conventional estimate of value with the reduction in physical risk and the increase in financial risk. These 2 elements form the “insurance value” with no health insurance, which can be calculated as the net monetary benefit multiplied with the variance of the probability of disease and a constant based on the marginal rate of substitution between “well” and “sick” states.\(^{10,11}\) The marginal rate of substitution relates to the consumer’s degree of risk aversion and intuitively reflects the amount of money a consumer would give up when healthy in exchange for gaining an additional dollar when sick. It rises when the consumer faces greater risks from illness. If there is access to health insurance, the increase in financial risk is partly or completely offset and we can calculate the “insurance value” with health insurance.

In Figure 4, we see the results of an example of cost-effectiveness analysis of biologics for rheumatoid arthritis.\(^{11}\) Results are expressed as net monetary benefit for 2 values of marginal rate of substitution (2.5 and 1.2), with the former representing a greater degree of risk aversion. An intervention that has value ex post reduces risk ex ante because the reduction in physical risk more than offsets the increase in financial risk. The concept underlying “insurance value,” (ie, an increase in expected utility with a reduced variance) also applies to quantifying the ex post health impact of a health technology. Health outcomes will likely vary across patients, even when we focus on clinically homogeneous subgroups. Consider 2 competing interventions with the same average survival—but one with much greater variability in survival—would be considered equivalent in a conventional cost-effectiveness analysis. For individual patients, however, this variability in outcomes represents uncertainty, and some may prefer one treatment over the other. Risk-averse individuals prefer the intervention with the reduced variability in treatment effects. If the first intervention results in an average 1.5 QALYs but with considerable variability across individuals in the population, the certainty equivalent might be 1.2 QALYs, whereas the second intervention with the same average QALYs yet less variability might be worth 1.4 certainty equivalent QALYs. The certainty equivalent is the number of QALYs that a patient would need to obtain to be indifferent between the comparator and the alternative treatment strategy.\(^{10}\)

This brings us to “value of hope.” The distribution of health outcomes is not only characterized by its variance but also by the skewness. Empirical research suggests that interventions may also have value when they provide an increase in the positive skew of the distribution of treatment effects.\(^{12}\) Even for risk-averse individuals, interventions for severe disease that increase the “right tail” of the distribution may still be incrementally valuable despite an increase the variation in outcomes.\(^{10}\) Patients with cancer may prefer the hopeful treatment option with the longer right-tail survival curve at the expense of a higher risk of dying earlier.\(^{12}\)

Source: Obtained with IV-RA model.\(^{11}\) MRS indicates marginal rate of substitution.
The recently presented framework by Lakdawalla and Phelps, where risk aversion related to the distribution in outcomes is integrated in the augmented cost-effectiveness analysis framework, facilitates investigating the impact on estimates of value, its relevance, and whether it can be estimated with credibility given the evidence typically available.6

Andrew Briggs: An Antithetical View
Although “fake” and “novel” are hardly antonyms—and it is not being suggested that the additional components of value identified by the task force are fake—it can be argued that neither are they novel or necessary.

The task force is to be lauded for concluding that cost-utility analysis and the QALY should remain front and center to value assessment in the United States. This is a hugely important endorsement of a methodology that has been refined over the last 40 years and is consistent with the original recommendations of the US Panel on Cost-Effectiveness Analysis, who also re-endorsed cost-utility analysis as the central method for assessing value in its 20-year update.5

Nevertheless, the task force did identify a number of additional components of value that they argued fell outside the standard cost-utility framework (Figure 1), although perhaps it is unfortunate that the net cost and QALY components were not represented as the central core of the flower. Representing them as petals alongside 10 other elements of value gives the impression that each could be equally important, but that is most likely not what the authors intended. Many of the elements of value were taken from the literature and by definition are not novel elements—rather they are identified as elements that are rarely included in a conventional cost-effectiveness analysis. Elements such as productivity, adherence, and reduction in uncertainty (the value of knowing) are routinely captured (at least in a societal perspective). Other elements, such as hope and fear, could legitimately affect individual decision making but are nonetheless fraught with difficulties in measurement as they relate to subjective experience and could be manipulated by the context. While both hopes and fears can be rational (as is the case with fear of COVID-19), they can also be groundless (one can “hope against hope”). Furthermore, the value of hope and the value of knowing can cancel each other out. Patients may value the chance of long-tailed survival, but if we develop a companion diagnostic that perfectly identifies patients who will benefit, do we have to remove the value of hope for those who now learn they cannot benefit from treatment?

The most important additional components of value identified relate to equity and severity of disease. Most individuals and societies actively value equity and would not want to see efficiency pursued at the expense of creating further inequality in the population. We also see evidence that severity of disease is important to many individuals and societies. Some of the recent debate about disability in the United States has focused on limitations of the QALY model in fairly reflecting capacity to benefit for disabled patients. In Europe, both Denmark and the United Kingdom have experimented with adjusting the QALY threshold to give greater weight to interventions that are targeted to those with a lower health endowment (ie, greater severity of disease).

The success of the cost-per-QALY approach has largely been because it has simplified the broader welfarist cost-benefit approach.

If we are to consider these additional elements of value, how should they be incorporated into the decision-making process? At least 4 possible solutions have been proposed. The task force suggested multicriteria decision analysis and augmented cost-effectiveness analysis as 2 approaches that could quantify additional value elements. While intuitively appealing, the devil is in the detail and the vast majority of examples of multicriteria decision analysis in the literature fall short of even the basic requirements required of economic assessment—particularly in relation to the cardinal utility property of the weights between attributes. The augmented cost-effectiveness analysis approach has much to commend it, but does have the problem of lack of comparability in the event that some analysts include additional value elements and others do not. Another approach is that decision-making bodies could adjust their decision thresholds to allow for other elements of value in the way that the Danes and the British have tried for disease severity. The final option is the status quo—to accept, as most jurisdictions that use formal cost-effectiveness methods do—that cost-utility estimates are only an input to, and not a substitute for, a deliberative decision-making process that allows for additional elements of value to be contextualized into the process without the need for formal quantification into the cost-effectiveness calculus.

In conclusion, the additional elements of value identified by the task force are a useful categorization of those things that can be captured in an economic appraisal and reflect the full economic analysis possible when conducting a full “welfarist” cost-benefit analysis. However, it is perhaps worth remembering that the success of the “extra-welfarist” approach in healthcare has been largely because it has simplified the traditional welfarist approach. Augmenting cost-utility analysis to reestablish these elements is equivalent to moving back to a welfarist approach. Far better is to accept the imperfections of cost-utility analysis and accept that a deliberative decision-making process can assess the wider elements of value. With apologies to Churchill, who once commented that democracy was the worst form of government except for all others that have been attempted from time to time, it has been suggested that cost-utility analysis is the worst form of economic appraisal for healthcare decision making—except for all the others that have been attempted from time to time.

Sarah Goring: Concluding Observations
The disparate views amongst the panelists provided an excellent opportunity for discussion and reflection on how value is captured in healthcare decision making. On the one hand, advocates for the...
STF’s approach argue for attempting the formal quantification—and even monetization—of additional value elements. On the other, skeptics would argue that additional value elements can be handled without formal quantification into the cost-effectiveness analysis calculus, and instead provide the context to a deliberative discussion of value to which cost-utility analysis remains core. Clearly, this is an important debate that we can expect to continue and from which our field will benefit.

Overall, each of the elements appeared to capture some aspect of real—not fake—value; however, their relative importance, their estimation, and how exactly they are incorporated into economic evaluation for healthcare decision making is still open to debate.

References
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