Towards A Vision for HEOR: Opportunities for Enhancement and Evolution
An ISPOR Health Science Policy Council White Paper

Original final version, July 28, 2023
Revised for posting, March 18, 2024

Executive Summary

I. Introduction
It is critical that Health Economics and Outcomes Research (HEOR) anticipate the needs of a changing healthcare environment and position itself to ensure relevance and impact. In the face of increasing demands for healthcare globally, and constrained resources to meet those demands, the importance of leveraging HEOR to inform healthcare decisions making has never been greater. This will enable improved outcomes, lower costs, better efficiency, and reduced health disparities While HEOR has made substantial contributions to population health and well-being in the last 50 years, defining the opportunities to contribute meaningfully in the future is essential.

This paper was developed by ISPOR Health Science Policy Council members and the ISPOR Chief Science Office to provide guidance on potential future scientific direction and related opportunities that are aligned with ISPOR's mission to improve healthcare decision making globally. This information will inform the ISPOR CEO and Board of Directors about scientific opportunities to be considered in the next ISPOR Strategic Plan.

II. History of HEOR
The modern-day healthcare research enterprise started in the 1940's and led to the methodologic evolution of randomized clinical trials (RCTs), epidemiology in the study of chronic disease etiology, and health services research. However, it wasn't fully recognized

until the early 1970's that the resulting evidence generated by this enterprise was rarely used to inform healthcare decisions. Health systems were inefficient and clinical practice varied across geographic regions with no underlying rationale.   Outcomes research was built on the foundations of health services research to address ways to improve patient outcomes and improve system efficiency. However, the discipline of HEOR emerged in response to health technology assessment (HTA) agencies that were established in the late 1980's to assess and appraise new pharmaceutical products. These agencies performed "value assessments", including cost-effectiveness analyses. In response, pharmaceutical companies and related consulting companies began to build expertise in HTA value assessments. At the time, the number of HEOR researchers was increasing but there was no professional home for them … this led to the formation of ISPOR in 1995 as a professional society created to support individuals and scientists working around value assessment, more commonly known at the time as pharmacoeconomics.

III. Barriers to uptake of HEOR.
A vital first step in mapping the journey forward for HEOR is acknowledging the reasons why the discipline has *not* been used as much – or as well – as it might have been. A targeted literature review identified five barriers to the applied use of HEOR:

1. information not relevant or appropriate for the audience;
2. needed information not available at the time of decision making;
3. complex information not seen to be transparent and therefore not trusted by decision makers;
4. lack of training in HEOR and its use at the decision-maker level; and
5. system or structural conditions not conducive to HEOR use.

IV. Addressing the barriers
Addressing the first three of these barriers requires better understanding and anticipation of the needs of specific decision makers - payers, physicians, or patients – and dedication to generating and tailoring HEOR evidence to be useful to them. In particular, greater attention to validation of decision analytic models' predictions of long-term outcomes using real world data (RWD) could lead to greater credibility. Further, improved educational outreach might improve decision maker confidence in the HEOR information they are receiving. Greater focus on the use of HEOR principles in health policy formation can help to reduce structural barriers.

IV. Opportunities for individual technology assessment

Individual technology assessment for medicines, genetic therapies, and devices has been the *forte* of HEOR to date and many opportunities, including the growing area of digital health care, exist to enhance what it offers. These can be summarized in four areas:

1. Promote methods-based international consensus about what constitutes valid and fit-for-purpose RWD and reliable real world evidence (RWE) as well as the utilization of that evidence;
2. Evolve HEOR evidence so that it is routinely used in payer and patient-decision-making for new products;
3. Strengthen the contribution of economic evidence (broadly defined) throughout the lifecycle, especially at an early stage to optimize product development decisions, at launch, and later, as new evidence becomes available; and
4. Grow capabilities for and use of HEOR evaluation of products in developing countries, particularly during the post-patent period.

A number of specific suggestions for further work in each of these areas are presented in this section.

VI. Opportunities beyond individual technology assessment
HEOR also has great potential, but often unrealized relevance beyond individual technology assessment, supported by work earlier this century by the Institute of Medicine in a "Translational Roadmap" that identified six aims and six domains for a "21st-Century Healthcare System". HEOR has significant opportunities to contribute by extending its core methods (modeling and economic evaluation, patient-centered research, RWE) to improve disease management, public health, and "whole health." Specific opportunities are:

5. Engage in research and educational content that addresses the largest areas of healthcare expenditures, including hospital care and physician services.
6. Engage in research and educational content that increases the use of HEOR evidence in clinical practice guidelines and quality of care measures.
7. Better understand factors that drive expenditure growth and develop recommendations to address them.
8. Adapt HEOR methods to population-based applications that cover all healthcare delivery in a specific high priority disease.
9. Apply HEOR to public health programs that address public health interventions on the clinical aspects of healthcare as well as broader issues of health behaviors, social and economic factors, and physical environment.

Collectively, these opportunities can support the development of a learning healthcare system that is structured to use new information more readily – to rapidly translate HEOR discovery,

for instance, into practical diagnostic and other policy decisions. They can also contribute to improvements in the affordability and economic sustainability of health care in general. This section provides more discussion in this regard.

VII. Conclusion

Opportunities for the enhancement and evolution of HEOR abound. Some involve greater focus on aspects of work already familiar to HEOR researchers in order to increase the usefulness of HEOR evidence to key stakeholders. Others involve applying HEOR principles to domains of health services research that have received less attention from HEOR.   Attention to both data and methods will be necessary for progress in many areas.

A cross-cutting theme for HEOR work in both individual technology assessment and the "Translational Roadmap" is developing consensus standards for RWD and RWE. The full potential for RWE's contribution to healthcare decision making can only be realized if data quality and the evidence generation process are seen as highly credible. ISPOR must continue to provide leadership and collaborate with other groups in this area.

The opportunities described in this white paper are not completely novel; the community of HEOR and health services research is large, knowledgeable, and sufficiently motivated to have undertaken work in most of these areas. Still, there is considerable room for growth and development in each of them. Limiting factors include funding, and an unequal distribution of HEOR researchers across the opportunities. As such, their identification and discussion here is most properly viewed as structured input for subsequent decision making about ISPOR's priorities to encourage work that is most critical to guide future health care decisions.

White Paper

I.   Introduction: Purpose, Rationale, And Strategic Context

ISPOR is a professional society whose members focus on the scientific discipline of Health Economics and Outcomes Research (HEOR).   The ISPOR Health Science Policy Council (HSPC) consists of current and past ISPOR leaders who provide organizational guidance on scientific issues such as research methods and its implementation through policy. This paper was developed by HSPC members and the ISPOR Chief Science Office to provide thoughtful guidance on potential future scientific direction and related opportunities that are aligned with ISPOR's mission to improve healthcare decision making globally. This information will inform the ISPOR CEO and Board of Directors with respect to scientific opportunities to be considered for the next ISPOR Strategic Plan.

The purpose of this white paper is to highlight opportunities for the field of HEOR to extend its work in ways that help ISPOR better fulfill its mission of "promoting health economics and outcomes research excellence to improve decision making for health globally." While HEOR has made significant contributions to healthcare policy and practice, the field and its influence continues to grow. ISPOR also has a history of successfully advancing HEOR-related work by extending the field's global reach (including applications in developing countries), championing educational content in new and important research areas such as health equity and social determinants of health, and encouraging research submissions on methods outside of traditional value assessment to its global meetings. This paper is intended to be a thoughtful examination of where HEOR has been impactful, why its use has been limited in some situations, and where its methods could be extended to enable even broader contribution and impact.

A previous ISPOR white paper explained how the confluence of the fields of health economics and outcomes research creates a powerful combination of scientific methods and endpoints to fully evaluate the clinical and economic value of healthcare interventions (ISPOR, 2019). To date, HEOR has most commonly been applied to new, individual technologies such as pharmaceutical products, including small and large molecule medicines, gene therapies, and medical devices, but less commonly to non-product-based health care such as physician and hospital services and health programs (Neumann et al, 2022). HEOR's use by decision makers has been strong in some contexts and weaker in others, for reasons that warrant further consideration. In addition, the breadth of potential healthcare applications for HEOR is much larger than evaluation (primarily economic value assessment and comparative effectiveness) of

individual technologies. While related fields like public health, health services, and health policy research have long studied such other aspects of healthcare, HEOR can augment these efforts by providing robust evidence, often complementary to what related fields offer, that is practical and useful to decisionmakers.

This white paper provides critical scientific input to the next ISPOR Strategic Plan by informing choices about how much focus and investment to put in areas beyond our traditional core work around the value assessment of new technologies.   Depending on the choices made, there is significant opportunity to stretch the boundaries of HEOR.   This work also builds on the *ISPOR Science Strategy* (ISPOR, 2021) and considers recent work and input from the Society's Special Interest Groups. The sections below provide background and historical perspective on the HEOR discipline, the barriers to implementation of new HEOR approaches, opportunities for enhancement and growth in value assessment of new individual technologies, and some opportunities for the continued evolution of HEOR.
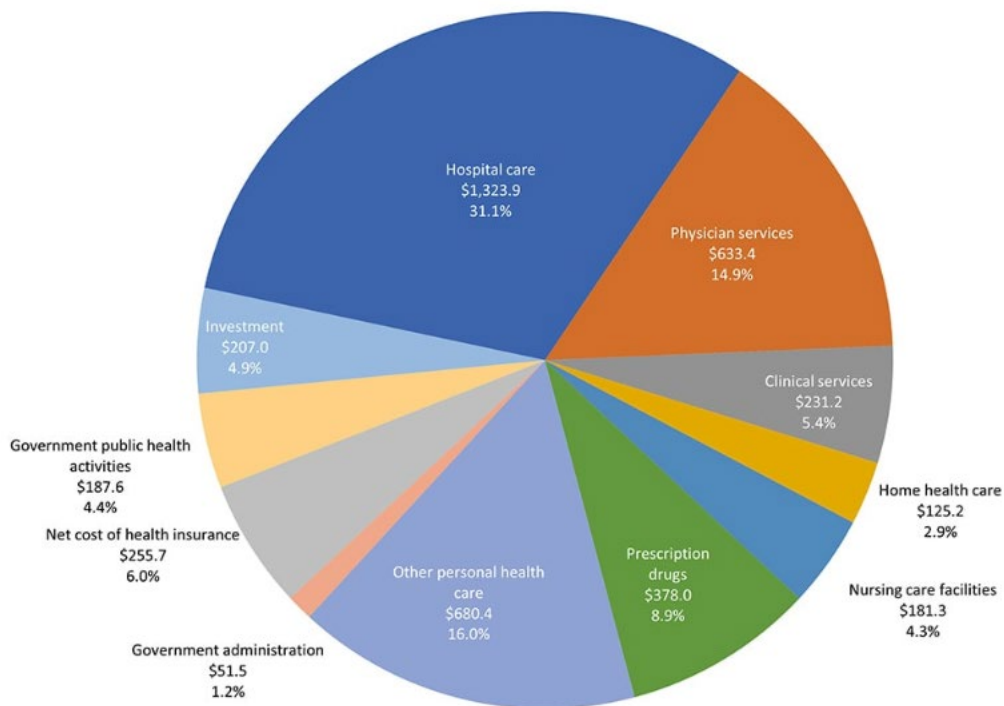
## II.	A brief history of HEOR

Health care spending and the current and potential scope of HEOR
HEOR research has historically focused on assessing the value of new healthcare technologies, notably pharmaceutical products and medical devices.   While this work is important, and these products can affect the need for other healthcare services, it represents only a small portion of healthcare costs.

Overall US healthcare spending in 2021 was over $4.2 trillion and the four largest categories of spending were hospital care (31.1%), other personal health care (16.0%), physician services (14.9%), and prescription drugs (8.9%) (Rama 2023).   While healthcare spending results from various studies can differ, expenditures on hospital care and physician services are consistently the highest categories of spending regardless of methodology or geography (OECD 2021). Moreover, many studies over several decades have demonstrated that healthcare delivery is inefficient and not always based on scientific evidence.

The U.S. spent $4,255.1 billion on health care in 2021 where did it go?

Hospital care
$1,323.9
31.1%

Physician services
$633.4
14.9%

Investment
$207.0
4.9%

Clinical services
$231.2
5.4%

Government public health activities
$187.6
4.4%

Home health care
$125.2
2.9%

Net cost of health insurance
$255.7
6.0%

Prescription drugs
$378.0
8.9%

Other personal health care
$680.4
16.0%

Nursing care facilities
$181.3
4.3%

Government administration
$51.5
1.2%

Figure 1. Distribution of US Healthcare Spending in 2021

Source: Rama A. National Health Expenditures, 2021: Decline in Pandemic-Related Government Spending Results in 8-Percentage Point Decrease in Total Spending Growth. American Medical Association Policy Research Perspectives, 2023.

The US situation is both interesting and concerning. It has both the highest healthcare expenditures per capita and per capita share of GDP of any high-income country, yet suffers from the lowest life expectancy at birth, and higher maternal and infant mortality rates, among other dismal health statistics. (Commonwealth Fund 2023). Its funding sources also do not match those in other countries, especially developing countries: "Health spending in low income countries was financed primarily by out-of-pocket spending (OOPS; 44%) and external aid (29%), while government spending dominated in high income countries (70%)." (WHO 2023). Developing countries conceptually include low income countries (LICs), low middle income countries (LMICs), and high middle income countries (HMICs). While use of pharmaceuticals and other individual health technologies have the potential to affect other areas of healthcare spending, the current focus of HEOR on those technologies misses the vast majority of healthcare spending. ***To realize the full potential of HEOR to help optimize healthcare decision making, its scope must be expanded beyond where it stands today.***

HEOR and its roots in health services research

The term HEOR emerged in the early 1990s, but its antecedents are much older. Our modern-day healthcare research enterprise started in the 1940's with the pioneering work of Austin Bradford Hill. In 1948, Hill reported the results of a randomized clinical trial (RCT) of streptomycin in patients with tuberculosis (Medical Research Council 1948). At around the same time, Hill also conducted etiologic epidemiology studies with Richard Doll on the association between cigarette smoking and lung cancer. (Doll 1950). This work stimulated research by others using similar methods. Health Services Research (initially called Medical Care Research) developed in the 1950's by using methods from epidemiology and health economics to study healthcare delivery.

Evidence requirements for pharmaceutical products were significantly strengthened in the early 1960's, triggered by birth defects that followed the market introduction of thalidomide. Regulatory agencies across the globe implemented policies that required safety and effectiveness evidence from "well-controlled studies" (e.g., most commonly RCTs) for market approval. This requirement further increased the use of RCTs in clinical research and observational methods in post-marketing surveillance where RCTs were not practical. Health services research also changed in the mid-1960's when Avedis Donabedian proposed a novel conceptual model in 1966 for evaluating health services and quality of care. The Donabedian model was later widely adopted by health services researchers (Donabedian 1988). During this same period, the seminal work by Kenneth Arrow on the role of uncertainty in the economics of medical care became a cornerstone for the emerging field of health economics (Arrow, 1963).

By the end of the 1960's, the healthcare research enterprise was thriving, but little was known about how research results were used in clinical practice. Archie Cochrane, a well-known and respected clinical trialist, published the textbook *Effectiveness and Efficiency* in 1972 in which he concluded that most healthcare decisions in the British National Health Service (NHS) were not supported by evidence and that there were a lot of inefficiencies in the NHS system (Cochrane, 1999)   Cochrane also noted that there was no repository for providers or health policy experts to go to for information on evidence to inform decision-making, which later led to the formation of the Cochrane Collaboration. Around the same time, Wennberg reported significant variations in healthcare expenditures and resources among 13 hospital service areas in Vermont (Wennberg et al 1973). For example, the probability of a tonsillectomy among children, before age 20, ranged from 16% to 66% in adjacent service areas with no underlying rationale for this variation. Wennberg did not attempt to address whether 16% was too low or 66% was too high, but in one or the other scenario, children were either under-treated or over-treated.   These early observations by Cochrane and Wennberg on the lack of evidence-based

decision making, healthcare inefficiencies, and clinical practice variation stimulated the formation of outcomes research as a new scientific discipline.

In the field of health economic evaluation, the work by economists and decision scientists in the US, Canada, and the UK examined how to evaluate the efficiency of health care technologies through cost-effectiveness analysis (CEA) (e.g., McKillop and Sheard, 2018). The term "pharmacoeconomics" was coined by Ray Townsend in the 1980's to characterize studies of pharmaceutical products. The use of the term "HEOR" as an abbreviation of health economics and outcomes research emerged shortly thereafter to allow both for broader applicability of these methods and to incorporate the outcomes research aspects of the work.

Driven by rising health care costs in the 1990s, health policy discussions began focusing on whether increased healthcare expenditures were providing commensurate benefits in terms of positive health outcomes. This led to the emergence of managed care organizations in the US that instituted formulary committees to assess the clinical and economic value of new pharmaceutical products as they entered the market and the founding of health technology assessment (HTA) agencies internationally. Among the first were the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia and the Canadian Coordinating Office for Health Technology Assessment (now the Canadian Agency for Drugs and Technologies in Health, or CADTH) in the late 1980's and then the National Institute for Health and Care Excellence (NICE) in the United Kingdom in the late 1990's, followed in turn by similar agencies in many more countries. Computerized billing in the U.S. and national health programs internationally led to the creation of large administrative databases to document diagnoses and health care service use as well as to inform HEOR studies. At the same time, interest was growing in patient engagement and patient-centered outcomes research.

ISPOR was founded in 1995 as a catalyst to advance the science and practice of HEOR globally. HEOR grew as an interdisciplinary field including, but not limited to, epidemiology, health economics, decision sciences, clinical research, biostatistics, outcomes research, operations research, psychometrics, and health technology assessment. This tapestry informed the vision proposed in 2001 by the U.S. Institute of Medicine in "Crossing the Quality Chasm" (IOM, 2001), which later informed the work on the Learning Healthcare System, (IOM, 2007). In a learning healthcare system, science, informatics, incentives, and culture are aligned for continuous improvement and innovation, with best practices seamlessly embedded in the care process and resources are allocated efficiently and fairly. This vision embraced both the encouragement of technological and process innovation as well as optimization of societal health with current resources. During the 21st century, widespread adoption of electronic health records and advances in the integration and analysis of larger and more robust datasets (i.e., "Big Data")

have enhanced the opportunities for HEOR and made the aim of achieving a LHS more attainable.

The next three sections focus on HEOR's application to individual technology assessment and how its contributions could be made more impactful. In section VI the paper turns to the broader realm of health services research with an eye towards areas where the use of HEOR could be expanded.

III.   Barriers to uptake of HEOR

Despite the growth in availability of HEOR evidence over the last few decades, its uptake for healthcare decision making has been far from universal. Hence the first task was to better understand the limitations to its use. Targeted keyword searches were undertaken from 2000 through to 1 December 2022 of MEDLINE for studies reporting limitations/barriers to use of health outcomes, comparative effectiveness, or real world data (RWD). The titles and abstracts identified in these searches were screened to identify articles likely to include barriers to the use of HEOR. After screening, full-text articles were obtained and reviewed. Results were highly US-oriented, reflecting the gap between availability and use of HEOR in the US. In some high-income countries, HEOR use is much greater (with some notable exceptions), while in developing countries, HEOR availability, while growing, has been much lower. Expert opinion was elicited and incorporated into the results of the review as supplement. Common themes around the barriers to the use of HEOR were reported within the literature and by experts (Figure 2).

Summary of Barriers to HEOR Use

Relevant information
Clinical trial design reported may not be appropriate for the audience. Data robustness and clinical nuances may be limited

Timely availability of information
Appropriate outcomes are not always available at the time of decision making

Skills/training to understand HEOR
Individuals who are critical to the decision-making process may have limited expertise, understanding, or ability to evaluate HEOR output

Presentation/communication of HEOR
Presentation of complex methods can drive decision makers to not trust the information. Be transparent

Systemic/structural conditions
Limitations due to policies, practices, and/or other norms and conditions associated with the healthcare environment including an inability to correct adequately for market and government failures

Figure 2. Summary of Barriers to HEOR Use

<u>Relevant information</u>
The first barrier often cited is specific to the relevance of the information that may be available to stakeholders at the time of decision making. This may include relevance of endpoints, clinical nuances between what data are needed versus what data are actually available, and where inferences can be made from the study population to the decision-maker's population. One common issue in valuing technologies is that the endpoints or outcomes available from a clinical trial may not be appropriate for a valuation study or the relevant audience (Deverka et al, 2020; Holtorf et al, 2012; Villa et al, 2013; Malone et al, 2018; Schumock et al, 2018). Specifically, clinical endpoints in trials may be appropriate for regulatory decision making but may be insufficient for valuing technologies in terms of costs and patient outcomes (Schumock et al, 2018). Understanding the impact of an asthma treatment on FEV1, for instance, does not necessarily relate directly to the need for a physician visit (i.e., a cost-driven outcome) whereas an exacerbation more directly translates to this need. Unless primary data are collected on medical resource use within a trial, analysts must make multiple assumptions to relate clinical endpoints to their impact on resource use and costs. Another similar example is ICD-10 codes not aligning exactly with trial endpoints, such that decision-makers may be hesitant to make linkages between them for modeling or costing for fear of being accused of performing off label promotion.

Further, with respect to the first barrier, it has been noted that in some cases there needs to be a greater understanding and alignment of comparative effectiveness research (CER) that matters to patients (Schumock et al, 2018). Often such CER evidence is not aligned with what the patient perceives as important, e.g., endpoints explicitly related to improvements in quality of life.

There was also some concern from payers about the relevance or credibility of evidence supplied by pharma sponsors. Examples suggested that it may be lacking transparency in methods/models or a biased selection of evidence (Mullins et al, 2011), that RWE evidence needs to be published and not "data on file" (Malone et al, 2018), and that budget impact evidence is seen as more important by sponsors than by payers, while the reverse is true for HRQL evidence (Bajaj, 2015).

Timely availability of information

The second barrier is that appropriate outcomes are not always available at the time of decision making (Deverka et al, 2020; Holtorf et al, 2012; Villa et al, 2013; Malone et al, 2018; Schumock et al, 2018). This will always be an issue for decision makers such as payers and clinicians when making policy or coverage decisions as these decisions need to be made before the technologies come to market and before they are able to demonstrate impact in real-world clinical practice (Villa et al, 2013; Schumock et al, 2018). We see decision makers using prediction methods (rightfully so) which often end up not being subjected to validation, even once RWE is available. Because a decision is already made, there is little incentive to validate the accuracy of prediction studies. As a result, there is no affirmation that the predictions used to make the decisions were correct. As such, there is a missed opportunity to improve on future efforts and to create buy in by those who are more skeptical or without expertise in the area.

Presentation/communication of HEOR

The third barrier to the use of HEOR is ineffective communication and/or presentation of research leading to lack of trust in the information. When presenting or communicating HEOR, it is important to understand the audience (i.e., who are the decision makers) and give due attention to providing clear descriptions and explanations. As noted earlier, many of the decision makers and beneficiaries of the efficiencies resulting from HEOR are payers and clinicians or patients who may not have the expertise to evaluate HEOR methods. HEOR needs to be put on platforms that are able to be accessed by and presented in a form that is understood by these stakeholders (Schumock et al, 2018: Malone et al, 2018). This may include conversion of technical materials into plain language summaries or other lay audience formats.

<u>Skills/training to understand HEOR</u>

The fourth barrier is the lack of training and/or skills to understand the HEOR and/or outcomes (Deverka et al, 2020; Holtorf et al, 2012; Villa et al, 2013; Morrato et al, 2013; Malone et al, 2018; Schumock et al, 2018). While true over the years, we have seen an increase in graduate and certificate programs focused on teaching methods commonly used in HEOR as well as the development of ISPOR's HEOR Competencies Framework (Pizzi et al, 2020). However, many decision makers have clinical backgrounds (e.g., physicians, nurses, and pharmacists) where their primary responsibilities are in treating patients. As such, they may have a limited exposure to/knowledge of these methods. It must also be acknowledged that the methods being applied are becoming more complex which can be difficult even for individuals who have the requisite backgrounds to understand.

<u>System/structural conditions</u>

Finally, a broader set of limitations to use of HEOR can be classified as "system/structural barriers." These are barriers that exist because of policies, practices, and/or other norms and conditions that affect the healthcare environment. They include payment systems that that do not incentivize providers to save costs (e.g., fee-for-service reimbursement may encourage overuse), to improve outcomes, or to implement processes to make treatment more efficient; resource constraints (e.g., financial) within various systems; healthcare system structures such as budget "silos" and the general fragmentation of care that creates disconnects for how health care in one domain affects costs and outcomes in another one; in some countries, notably the US, lack of an integrated health information technology infrastructure and requirements for data collection; or the nature of RWD such as the constructs and governance around the information which make it difficult to use. In developing countries, the availability of data for HEOR work is often much lower (e.g., Gulácsi et al 2012; Mangoya et al 2023). There are also barriers to implementation of policies or decisions due to general knowledge, attitudes, beliefs, and self-efficacy.

IV.   Potential Approaches to Increase the Use (and Impact) of HEOR

Section III has summarized some of the barriers to the performance, understanding and application of HEOR to healthcare decision making. In this section, we highlight examples of approaches that might lower or even eliminate these barriers going forward. In subsequent sections, we provide more specific ideas about how HEOR evidence can be generated throughout the lifecycle of a new healthcare intervention.

<u>Improving relevance and timeliness of HEOR information</u>

Addressing the barrier that HEOR information may not be relevant to a specific decision maker, it is important to understand that there are many ways that decision analyses involving HEOR can be performed and presented to health care decision makers. These include: 1) whether or not to develop a new intervention; 2) market access and reimbursement; or 3) about individual use of the intervention. For HEOR information to be useful it should be available at the time decisions are made, focus on specific information needs, and be presented in a format that is readily understood. This may mean presenting only a subset of outcomes that are relevant for a particular decision context or developing models that synthesize the available data into outcomes that are relevant. Table 1 presents a listing of three common types of health care decision makers and their objectives as well as their HEOR information needs.

Health Care Decision Maker	Primary Objectives	HEOR Information Needs
Those developing new healthcare interventions (commercial or public enterprises)	Allocate funding to research and development (R&D) for different conditions on the basis of expected financial and/or population health outcomes	Potential return on investment (ROI) based on achievable price and projected market uptake given expected health and QOL outcomes gains versus alternative interventions
Those responsible for reimbursement and access to new technologies or services in the healthcare system within a country through government funding or insurance	Allocate available funding or maintain acceptable insurance premiums in such a way as to maximize population health, (death rates, quality of life) and safety while ensuring health equity	Efficiency of new intervention relative to standard care (e.g. ICER); expected health and quality of life gains; improved functional status; and budget impact and/or opportunity cost for other healthcare interventions or other uses of government funds
Physicians or other providers of healthcare services; patients with indicated diseases and their caregivers or general population at risk of indicated disease, based on shared decision-making	Maximize health, safety, convenience, quality of life and functional status for recipients with indicated disease while ensuring affordability	Expected health, quality of life gains and improved functional status, tailored when possible to the individual patient situation, compared with standard of care, and acceptable out-of-pocket expenditures and convenience for patients and caregivers

Table 1. HEOR Information Needs for Decision Makers With Different Decision Contexts

There are several ways that HEOR information for drug, devices and diagnostics has been packaged and presented to different health care decision makers in the last few decades. Most often the focus for HEOR has been those decision makers working in the context of reimbursement or access who make decisions at the time that a technology is first approved for use. Because clinical information on use in standard practice is limited at the time that a technology is first approved for use, the resource use and outcomes data collected from patients are extrapolated and used in a decision analytic model to provide estimates of the direct and indirect costs and health outcomes over the disease lifetime with primary outcomes of cost-effectiveness and budget impact . ***However, some of the barriers presented in Figure 2 might be ameliorated with greater attention to validation of the decision analytic models' predictions of long-term outcomes using RWD***.

Since disease treatment patterns and individual patient responses to the disease and its treatment vary, extrapolation models include many uncertain inputs and can also be quite complex mathematically. This limits the ability of a decision maker who is not a technical expert to understand the model structure and may reduce the credibility to them because of the uncertain model outputs. One possible solution is to create disease-specific cost-effectiveness and budget-impact models that have been validated against clinical trial and/or long-term observational data for the disease of interest and use it for all new products in the disease area to estimate the likely long-term impact of the new intervention. (Eddy et al, 2010; Graham et al, 2012; Dunlop et al, 2022); This has been done for diabetes - see Mount Hood Challenge (Palmer et al, 2013; Tew et al, 2022). Such an approach is currently underway for modeling the impact of vaccines for respiratory syncytial virus (RSV) infection using observational data on the burden of illness in the absence of a vaccine (Wildenbeest et al, 2022; van Wijhe et al, 2022). The expected health and cost outcomes from these prediction models can then be compared with those observed for those receiving a vaccine.

An alternative method to validate a decision analytic model is to implement a long-term follow-up program and risk-sharing agreement as was done in the UK for Multiple Sclerosis when Interferons were first indicated as disease modifying agents (Palace et al, 2019). The UK scheme included agreement with the manufacturers that they would reduce the annual price or pay back money to the National Health Service if the long-term follow-up did not confirm the decision analytic model estimates using the clinical trial data. That study has taken over a decade and has confirmed the modeling estimates of the long-term health outcomes that were extrapolated from the clinical trial data. Long-term follow-up of the outcomes of new

interventions with or without risk-sharing agreements have the potential to use RWD to validate extrapolations that may result in greater acceptance of HEOR data by decision makers.

Improving presentation and communication of HEOR information

Decision analytic models may be very complex and difficult to understand by those making decisions about use of a new intervention for individual patients. There are alternative ways to present the HEOR data that are of interest to them for decision making that might make it more acceptable. For example, the "Second Panel" for Cost-effectiveness in Health and Medicine (Sanders et al., 2017) recommended creating an Impact Inventory which is a listing of all the different changes in costs and outcomes and their sources that are associated with use of a new health care intervention. The items listed in the impact inventory can include both those that are directly observable at time of launch such as changes in short-term health outcomes, quality of life, functional status, and resource use as well as those that might be estimated using extrapolation in a decision analytic model, for example incremental quality-adjusted life years or incremental cost per quality-adjusted life year gained. This impact inventory could also include other observed or estimated outcomes from using the new intervention including indirect costs and family burden and other elements included in the ISPOR Value Flower and estimated using available data and modeling techniques (Lakdawalla et al., 2018). While not a simplification per se, the impact inventory, particularly if summarized in a "data dashboard" format (Neumann, 2021), allows a physician or patient who may not fully understand a complex decision analytic model to select those outcomes of greatest importance and credibility to them and to apply their own judgment when reaching a decision on use.

Healthcare decisions between a patient and their physician should ideally be informed by relevant scientific evidence.   The challenge for patients is that evidence from studies is reported as population averages and is not meant for informing individual patient decisions. Indeed, there may be circumstances where a study shows that Drug A is superior to Drug B based on study population averages, but in some patients, Drug B may be superior to Drug A based on heterogeneity of treatment response (Kravitz 2004). ***One area of potential opportunity for HEOR is to identify better methods for answering the question that individual patients are interested in … "What is the best drug (most effective, safest, etc.) for me?"***   For example, in a large health system, could the patient be matched to other patients with similar genotypic and phenotypic characteristics to see how they responded to treatments?   If so, could that better inform treatment decisions? Are the current data systems capable of providing this type of analysis in real time during the patient visit? The opportunity is for HEOR scientists, and ISPOR, to engage patients for the purpose of improving shared decision making and better informing patient's individual treatment decisions.

<u>Addressing need for training and/or skills to understand HEOR</u>

The fourth barrier cited by decisionmakers was their lack of training and/or skills to understand the HEOR work. Addressing the three barriers as discussed above may improve the comprehensibility of HEOR evidence, but additional training would still be helpful. Education of stakeholders is an important part of ISPOR's Education and Training pillar, detailed in our *2020-24 Strategic Plan (ISPOR, 2020)*. As the HEOR field evolves, the activities included there will need to evolve accordingly; more collaboration with local trainers that are familiar with their health care systems and their organization will be needed.

<u>Addressing system/structural barriers</u>

The final type of limitation discussed in section III was "system or structural barriers". As a constellation of political, financial, regional, administrative, and behavioral factors, they are not feasible for HEOR to address unilaterally -- but HEOR may have a role to play -- and some areas of progress can be seen. For example, a policy proposal put forward to move the US away from fee-for-service care (one of the more prominent systemic barriers in a major country) has been making some progress in state Medicaid programs (APM Framework, 2016). Efforts like Sentinel in the US, the European Health Data & Evidence Network (EHDEN) in the European Union, the Observational Medical Outcomes Partnership (OMOP) and others are gradually improving the quality and usefulness of RWD; more general availability of RWE to researchers is still needed. Organizations like WHO, the World Bank, and others have helped developing countries establish health care infrastructure and programs where HEOR principles are being utilized. The presence of HEOR principles and experts can be seen as one of the incentives for modifying systemic barriers, in that HEOR can then be used to improve health care decision making. ***Thus, it seems important for increased adoption of HEOR principles for ISPOR to stay actively involved in and help shape those efforts.***

**V.   Opportunities for enhanced generation and use of HEOR for individual technology assessment**

<u>Current use of HEOR by Product Phase</u>

As indicated earlier, the principal use of HEOR has been support for initial market access – principally in HTA for pricing and reimbursement (P&R) – of new products. However, the product cycle begins much earlier than launch and extends to genericization and beyond. While HEOR has been applied at all stages of the product cycle, the increasing scrutiny of drug budgets and prices worldwide, as well as the demand for drug availability as part of universal health care, suggests that greater use of HEOR evidence has a demonstrable impact on product strategy. This is especially true during early product development by early value assessment and evidence generation planning, during the product introduction period by reducing clinical

and economic uncertainty, and later on by monitoring and guiding long-term product utilization to and beyond loss of patent life.

In order to identify the major opportunities for enhanced use of HEOR, we first considered the major HEOR activities and to what extent they are currently used across the product lifecycle. Figure 3 shows the phases of product development where HEOR work is currently used, with darker shading representing more extensive current use.

Epidemiology is already used early in the product life cycle to understand disease burden and potential market size for specific indications. Of course, pharmacoepidemiology has historically been used to generate evidence for regulatory decisions, including drug safety purposes, REMS, labeling, and product withdrawal. HEOR has generally included some epidemiological work to generate evidence to support market access decisions. The use of data science and real-world evidence to support our understanding of effectiveness outside of clinical trial settings has increased over recent years, mainly in later phases of development and adoption. This is partly in response to the increasingly recognized divergence in efficacy and effectiveness, and also to address prevailing uncertainty due to narrower treatment targets and/or accelerated approval pathways. Some modeling is done early and late in the lifecycle, but its primary use is in late-phase development to support the initial HTA and market access phase, and to some extent for P&R support. Other types of health economic evaluation (e.g., cost-effectiveness analysis alongside RCTs) are also employed during the same times and for the same purposes as modeling. Health outcomes and PRO research, while sometimes planned during pre-clinical phases, usually is most seriously pursued once clinical development begins, is used for initial product dossiers, including product labeling, and may be continued in Phase IV work. Pricing support from HEOR is also heavy during clinical development and launch, with contracting support after launch is more dependent on whether there is a need for outcomes-based or other types of risk-sharing agreements. Other potential contributions of HEOR, for health policy analysis, implementation considerations, and environmental impact, are not as intensely pursued (yet) as more standard types of HEOR work and are generally considered post-launch if at all.
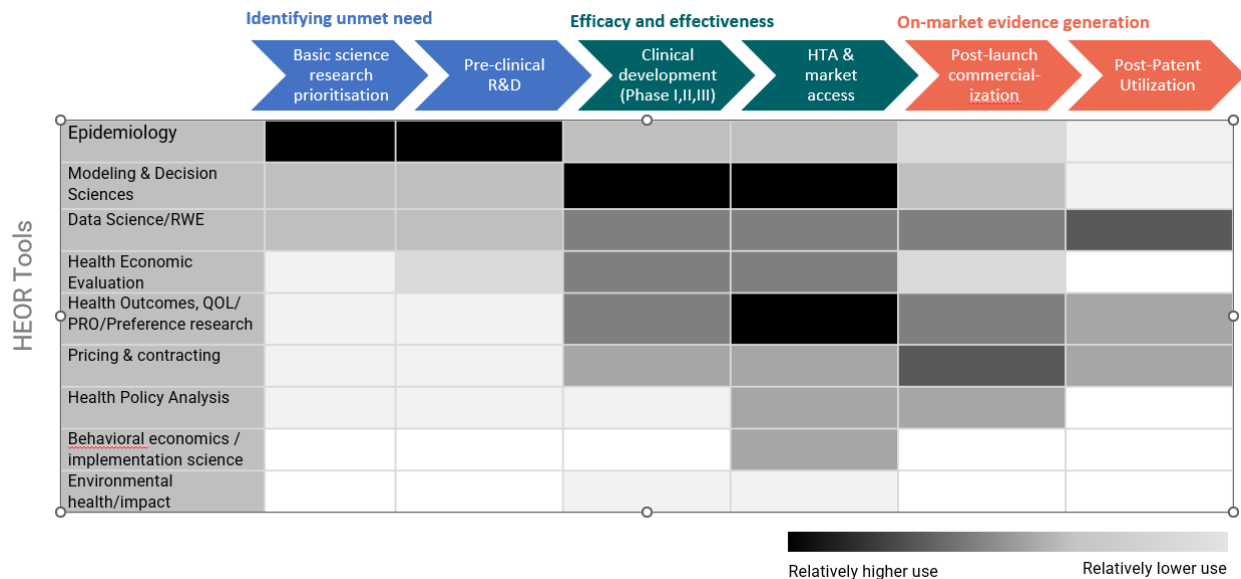
Figure 3. Current Use of HEOR by Product Phase

HEOR has evolved over the years, but there is still room for considerable extension and enhancement of our discipline within the development, assessment, and utilization of medical treatments. Extended use of HEOR tools seems a natural evolution but is also being accelerated by external factors, including changes to drug development and the nature of innovative therapies (e.g., higher cost, targeting more precise patient groups or addressing high unmet needs leading to earlier approvals) which are often leading to increased uncertainty associated with treatment safety and effectiveness. In addition, affordability challenges are ever-more concerning for health policy stakeholders, and changes to population and environmental health are such that the considerations of decisions-makers relating to these are evolving. Moreover, there are more healthcare data now than ever before, which enhances the opportunities to do more to predict, capture and monitor treatment effectiveness and impact.

Opportunities for extended use and impact of HEOR

Opportunities for extended use and impact of HEOR are summarized in Figure 4. Four main opportunities emerge:

1. Promote methods-based international consensus about what constitutes valid and fit-for-purpose RWD and reliable real world evidence (RWE) as well as the utilization of that evidence;
2. Evolve HEOR evidence so that it is routinely used in payer and patient-decision-making for new products;

3. Strengthen the contribution of economic evidence throughout the lifecycle – early on to optimize product development decisions and later on to support optimal reimbursement and uptake; and

4. Grow capabilities for and use of HEOR evaluation of products in developing countries, particularly during the post-patent period.
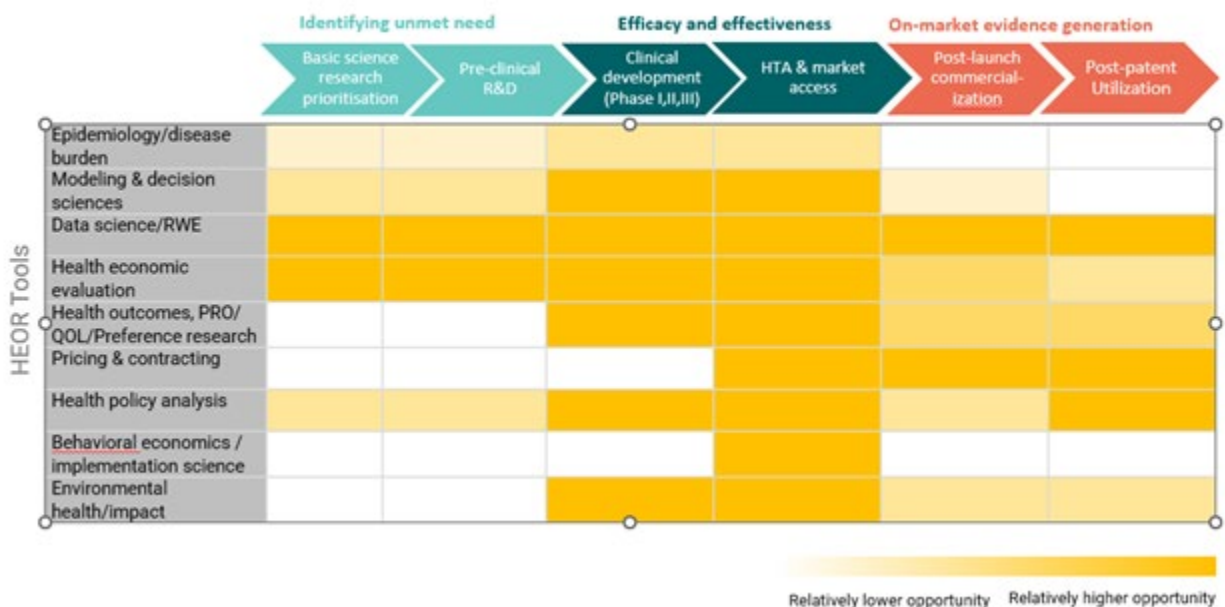
Figure 4 – Opportunities for extended use and impact of HEOR

Opportunity 1: Promote methods-based international consensus about what constitutes valid and fit-for-purpose RWD and reliable real world evidence (RWE), with greater attention to evidence from digital health data, as well as the utilization of that evidence

RWE has long been a key area for HEOR and its potential for making even greater contributions to health care decision making is strong. There are active ongoing developments by both regulatory agencies in the U.S. and Europe to develop criteria for assessment of whether RWD is fit-for-purpose and what constitutes reliable RWE. ISPOR has partnered with other organizations (especially the International Society for Pharmacoepidemiology and Duke Margolis Center for Health Policy) in recent years on a number of efforts that have advanced this agenda. Specific areas for further work, classified into data quality and availability, methods, and process/policy topics, are:

Data quality and availability

- Increasing appropriate access to high quality and credible RWD sources to support a wide range of researchers and research endeavors, collected and accessed with proportionate and appropriate data governance which both protects patient privacy and allows access to data for research purposes;
- Advancing and creating standard methods for auditing and validating RWD elements;
- Better linkage validation and appropriate use of data and data linkage opportunities from diverse sources across health and non-health sectors, particularly from digital health sources, e.g., characterizing lifestyle factors to estimate future incidence of a condition, as well as social determinants of health for evaluating health equity;
- Contribute to the creation and incorporation of core outcomes sets, including patient relevant outcomes such as symptoms, functional status, quality of life, and more holistic measures of health into electronic health records;

Methods
- Advancing analytical methods to minimize bias and appropriately characterize uncertainty as well as to promote agreement on when it is appropriate to draw causal inferences from RWE derived from observational studies;
- Development of criteria for the appropriate use of natural language processing and machine learning in creating research-ready data from health care encounters;
- Refinement and validation of artificial intelligence programs for reliable use to inform medical decision making;
- Refinement of methods not only for duplicating RCT results but also for extrapolating those results to populations or subpopulations that differ from the RCT sample (e.g., RCT-DUPLICATE, OPERAND);
- Further development of methods and processes that enable and validate the use of wearables, digital app, and other digital health data for research purposes;

Process/policy
- Making transparency the norm, including use of protocol templates and study pre-registration, to increase trust in RWE (e.g., Berger et al, 2016);
- Refinement of use of external control arms to further their regular use by both regulatory agencies and HTA bodies;
- Evaluation of how regulatory policy as well as coverage and reimbursement and other institutional settings (e.g. scope of practice laws) affect access and use of RWD; and
- Development of new relationships and partnership opportunities with other organizations in this space, such as American Medical Informatics Association and Society for Clinical Trials.

With ever-expanding opportunities to collect more data, there is an onus on all stakeholders to make the most of those opportunities, while doing so in a credible and appropriate way. One of the areas gaining most attention at present is the use of RWE in regulatory and reimbursement decision-making, with several agencies or working groups releasing guidance (US FDA, 2020; REALISE, 2020; HMA/EMA, 2022; NICE, 2022; CADTH, 2023). This represents a necessary step toward developing consistency and transparency in the generation and use of RWE. There is a growing case history of use of RWE-based external control arms for initial regulatory reviews of new oncology and rare disease products, though with considerable variability in how well the evidence is accepted (e.g., Jaksa et al, 2022; Purpura et al, 2022; Bakker et al, 2022).   New efforts could include reaching out to other initiatives involved in shaping RWD-RWE standards (e.g., CIOMS working group, ENCePP, ICH) to promote development of consensus standards Clearly, much more work needs to be done, especially on data quality but also on methods, to generate RWE that is routinely seen as useful for decision-making and available at the point of care; ISPOR should continue to provide leadership in this area.

Many of these opportunities outlined above are not topics that HEOR can address unilaterally – some require collaboration with other disciplines, some probably need to be led by other disciplines. However, in each case we believe that HEOR involvement would be important to development and implementation of these topics for meaningful use in many aspects of healthcare decision-making. These opportunities and others apply across different parts of the product cycle as well as across industry, academic, payer, patient, employer, and government sectors.

Opportunity 2: Evolve HEOR evidence so that it is routinely used in payer and patient-decision-making for new products

The role of HEOR in general during the key phases of late clinical development and early market access also can be enhanced. In addition to the RWE and economic evaluation points mentioned above, as well as the points raised in section IV above, specific areas of progress include:

- Development and use of more validated, open-source disease models would allow payers and others to verify their results and adapt them to their own populations with more confidence (Pouwels et al, 2022);
- Adapting economic evaluation to alternative trial designs, such as adaptive or basket trials (in conjunction with organizations like SCT);
- Advancing the use of standard Patient-Centered Outcome Measures/Core Impact Sets in RCTs can help make trial results more meaningful to both payers and patients, and can

also make indirect treatment comparisons and systematic reviews more comparable across products (National Health Council, 2022; ICHOM 2023);

- Development of methods and data collection to reduce uncertainty about product safety and effectiveness and resource implications across longer time periods and broader populations to better inform pricing and utilization;
- Increasing focus of epidemiological methods to detect differences in baseline risk across population groups, with an emphasis on understanding new product impacts on health equity;
- Support for information-sharing across jurisdictions for economic evaluations based on the transferability of clinical and real-world patient data; and
- Collection and preparation of data that may be useful to support clinical guideline development, quantitative benefit-risk assessment, or other post-launch uses.

Per the discussion in Sections III and IV above, there are several areas where HEOR evidence for new products can be improved for use by decision-makers. Given that registration trial results are the primary outcomes evidence available at product/technology launch, disease-by-disease attention is important to ensure that those results are reliable indicators of real world outcomes most meaningful to patients and payers. This makes it important for HEOR to engage with patient-focused drug development and Core Outcome Set work. On the health economics side, the more that economic models can be calibrated and validated with real world results, the greater will be the trust given their predictions at launch. Several HTA agencies (NICE, ZIN, CADTH, ICER) are beginning a working group to facilitate knowledge sharing about the development of disease-specific reference models. Clearly, more resources need to be devoted to model validation efforts, perhaps to the creation of a formal, independent model assessment group. Post-launch comparative effectiveness research (CER) using RWD has been done for many years, but there has been growing interest in methods for CER relatively soon after launch for rapid-cycle HTA and evidence development. It can help resolve initial uncertainty about product effectiveness and cost impacts as part of initial risk-sharing agreements and inform mid-lifecycle reconsideration of pricing or reimbursement (e.g., Gagne et al, 2013; Schneeweiss et al., 2016, Fleisher et al, 2023).

Opportunity 3: Strengthen the contribution of economic evidence throughout the lifecycle, especially *earlier on* to optimize product development decisions and *later on* to support optimal reimbursement and uptake

Economic evaluation also has considerable potential for expanded scope in product planning, support, and assessment, both internal and external to life sciences companies. Examples of areas for further work that include but are not limited to:

Early product planning

- Early evaluation to guide development that better anticipates and designs value-based, cost-effective disease solutions; do preliminary value calculations to help with expected NPV (particularly reimbursement risk adjustments) calculations for go/no-go decisions, which can also be updated along the product lifecycle (e.g., Girling et al 2015; Grutters et al 2018; Kirwin et al, 2022, Rodriguez Llorian et al 2023);

- Creation of an early data development plan, including RCT, health preference, and RWD evidence planning to support more robust value assessment; more guidance may be needed here;

- Development of early models to explore potential costs and effectiveness of drugs or their equivalent in late development could help the design and data collections of trials, as well as guide additional research to fill information gaps on some valuable parameters required to properly assess the value of the interventions;

Pricing and market/patient access support

- Collaboration between HEOR and market access groups on issues related to pricing, e.g., multi-indication pricing, response to international reference pricing, equity-based tiered or differential pricing to improve access in lower-income countries, optimizing launch sequencing, etc.;

- More research on the implications of pricing especially as it relates to alternative contracting and payment mechanisms such as coverage with evidence development, performance-linked reimbursement, and adaptive reimbursement (Garrison et al, 2016);

- Improvement of research studies done for market access and pricing studies to better understand how markets will respond to policy changes as well as to redesign markets with better incentives, e.g., to eliminate low value care, or to incentivize introduction of generics post-patent expiry (e.g., McElwee 2023).

Methods

- Develop practical methods to address clinical and statistical heterogeneity in value assessment using RWD (e.g., Grutters et al, 2013; Segal et al, 2023);

- Continued research on, measurement of, and testing in decision-making of novel value elements in the ISPOR Value Flower (e.g., Neumann et al, 2022);

- Consideration of use of cost-benefit analysis, as used in program evaluation, when fixed costs, externalities, equity, and other societal considerations (those difficult to incorporate into individual cost-effectiveness comparisons) are important;

- Develop methods to determine the societal return of investment, which includes the impact on carbon footprint and climate justice as guiding principles, based on a better

understanding of factors that drive expenditure growth and welfare and develop recommendations to address them;

<u>Broader applications</u>

- Increasing focus on evaluating the class of drugs rather than individual drugs once there are several similar drugs in a given class;
- Evaluation of more holistic measures of health, including comprehensive measures of value, patient-centered care, interconnectedness, prevention and early intervention, and health equity;
- Extending CEA done for individual products to encompass their use with other products or services within clinical guidelines (e.g., Garrison 2016), treatment sequencing (e.g., Hirsh and Singh 2020), and care pathways (e.g., Everink et al 2018); and
- Refinement of methods for use of RWD in economic evaluation to support post-launch prioritization and sectoral resource allocation decisions (e.g., Malone et al, 2018; Lee et al, 2021).

Health economics work can inform the internal strategic decisions of producers or external decisions of those using or paying for the producers – sometimes both. Internal strategic work may or may not be seen as ''scientific'' but is very much within the domain of economics in the broader sense. Whether such work is done for producer or consumer or both, it is important that it be done using reliable data and methods; poor analysis rarely leads to good decisions, while well-informed decisions by all market participants, in general, support more efficient innovation and utilization. Regular monitoring and, when useful, adoption of methods developed in other branches of economics will add to the HEOR toolkit.

Opportunity 4: Grow capabilities for and use of HEOR evaluation of products in developing countries, particularly during the post-patent period

The data and monitoring of post-patent product evaluation is essential to ensure positive and cost-effective health outcomes, particularly in developing countries (e.g., Kirwin et al, 2022). However, there is an increasing interest across developing countries in the use of HEOR in decision-making. Often its use has wide variation and limited applicability (e.g., Mangoya et al, 2023). Given the current focus on prioritizing and costing essential benefits packages for universal health coverage, many of which include interventions of post patent individual technologies, the timing for greater emphasis on HEOR training and utilization would be propitious. In addition, to promote technical self-reliance and sustainability, a growing number of countries observe ongoing HTA guideline development efforts. Promoting HEOR capacity building in developing countries is also a major element of ISPOR's Science Strategy and is already an area of work in some ISPOR chapters (see Content Analysis for 2022 ISPOR Chapter

Reports, May 30, 2023). Working with ISPOR chapters to foster collaborative relationships with the respective Ministries of Health may help advance the use of HEOR as HTA becomes institutionalized in some countries.

While the role of health economics in product evaluation and setting benefits package is generally well-appreciated (e.g., Drummond et al, 2023), the contribution of patient reported outcomes (PRO) and health-related quality of life (HRQL) research may not be as well delineated. However, post-patent research on PRO/HRQL could provide better understanding on how the drugs/devices impact disease management and specific patient groups that could extend beyond the original RCT populations.

The implementation of PRO research during the post-patent phase faces several challenges and knowledge gaps, therefore presenting opportunities. They include:
- Patient understanding of the purpose of PRO research is limited, because the concepts or tools used in PRO research may not be understandable to patients, particularly less health-literate patients; more focus on simple functional status and symptom measures may result in better acceptance. Public health education on PROs to patients is lacking and/or limited and varies considerably from country to country (for a US example, see https://www.youtube.com/watch?v=mO1mWBIB50U). The development of regional and language-specific platforms to educate patients about PRO research is urgently needed. (Katz et al, 2021; Taylor et al, 2021).
- Standardized guidance on conducting PRO research during the post-patent phase, particularly in developing countries, is needed. Since PROs are subjective measurements, they are affected by many external factors including mood, time, socioeconomic status, environment, and interactions with healthcare providers. While guidance on conduct of research during regulatory phase RCTs is available (FDA, EMA), post-patent treatment population situations and can be quite different and involve adapted considerations.
- Incentives for the pharmaceutical industry and/or health authorities to invest in PRO research during post-patent phase are needed, because the commercial incentives driving this research during regulatory and on-patent phases are considerably reduced. Much may depend on the mission, vision, and readiness of local health authorities to support such research.
- Support for big data development for PRO research globally is also needed. While there is awareness of this need in developed country databases (e.g., Sentinel, DARWIN-EU), much more work is needed to make the common availability of PRO data a reality, especially in developing countries.

- Strategically-driven collaborations with organizations like the World Health Organization, the World Bank, donors like the Gates Foundation, the Institute for Health Metrics, and many others, as well as with ISPOR country chapters, are likely to be important to this work.

This section has highlighted several broad areas of opportunity to improve how HEOR can be impactful during the product lifecycle, each with many specific points of focus. For the most part they are not completely "new" ideas, yet much work – both in their methods and their implementation - remains to be done to achieve their full potential. We now turn to opportunities for HEOR outside the individual technology product cycle.

VI.   Opportunities for HEOR beyond individual technology assessment

The purpose of this section is to explore areas of potential opportunity for HEOR (and ISPOR) beyond value assessment of individual pharmaceuticals and medical devices. To set the stage for this discussion, we provide some additional historical context.

Dougherty and Conway (Dougherty and Conway 2008) from the US Agency for Healthcare Research and Quality and the Centers for Medicare and Medicaid, respectively, developed a Translational Research Roadmap for US governmental healthcare agencies, and grantees, to categorize their research across a broad research spectrum. This Roadmap has been used extensively in the US and we are using it in this section in order to better highlight where the opportunities are. The Roadmap diagram is depicted as linear but it's meant to be cyclical – from bench basic science to bedside and back to bench.   The authors highlight the fact previously made that the healthcare research enterprise has been very successful in generating evidence from bench science (T0 and from clinical efficacy research (T1), somewhat successful at generating comparative effectiveness and health services research (T2), and not as successful at studying strategies for using scientific evidence to improve quality of care and lower costs in health systems (T3) or for population health, public health and prevention. Figure 5 below illustrates this Translational Research Roadmap.   The diagram itself has evolved since initial publication - now basic biomedical "bench" science is referred to as T0 and public health and population health is referred to as T4.

The Translational Roadmap to Transform US Healthcare
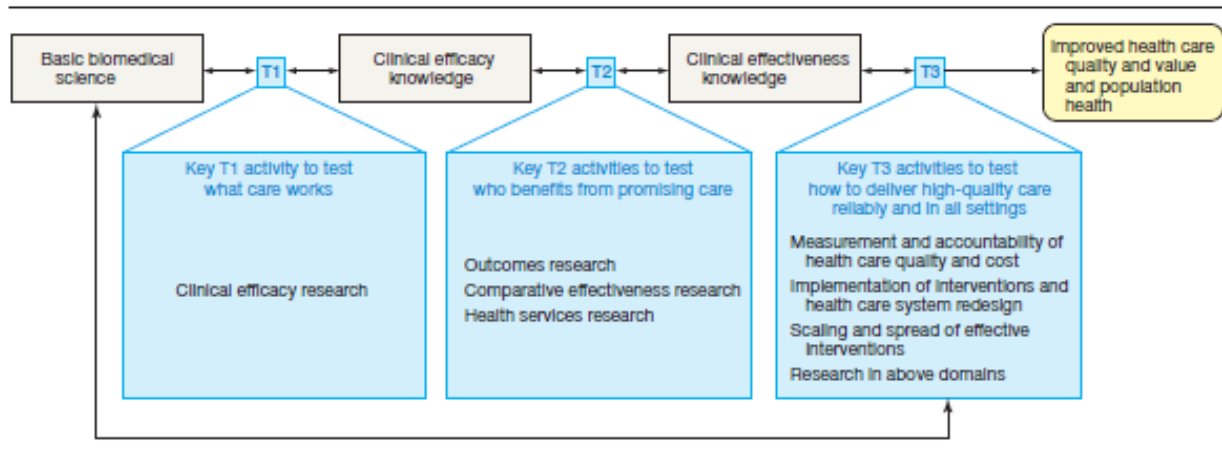
Figure 5

HEOR scientists have historically worked to inform decisions in drug development (T1 research) and specific areas to study "who benefits from promising care" (T2 research), but not as much in healthcare delivery (T3 research) or quality of care, public health, and population health (T4 research). The section below provides some background on the types of T3 and T4 research that would be aligned with HEOR.

The U.S. Institute of Medicine (now the National Academy of Medicine) published a number of reports from the early to mid-2000s on quality of care, improving outcomes, and lowering costs in the U.S. healthcare system. Two of these reports, those thought to be most relevant to HEOR, are described below. While some of the IOM work may be specific to the U.S. healthcare system, we have attempted to identify certain findings that have broader application and are relevant to the Visioning Project.

Crossing the Quality Chasm was published in 2001 by the IOM and was a blueprint for healthcare reform efforts to address healthcare issues related to quality of care, cost of care, including effectiveness and efficiency, value-based healthcare, and the development of "learning healthcare systems" (Institute of Medicine 2001). The report identified six aims for a "21st-Century Healthcare System." These six aims are likely relevant in other geographic areas and provide additional guidance for potential opportunities for HEOR. They are:

1. Safe – avoiding injuries to patients from the care that is intended to help them;
2. Effective – providing services based on scientific knowledge to all who could benefit and refraining from providing services to those not likely to benefit;
3. Patient-centered – providing care that is respectful of and responsive to individual patient preferences, needs, values, and ensuring that patient values guide all clinical decisions;

4. Timely – reducing waits and sometimes harmful delays for both those who receive care and those who give care;
5. Efficient – avoiding waste, including waste of equipment, supplies, ideas, and energy; and
6. Equitable – providing care that does not vary in quality because of personal characteristics such as gender, ethnicity, geographic location, and socio-economic status.

Following the IOM Quality Chasm work, the IOM Roundtable on Value and Science Driven Healthcare published a series of workshops on the need for "learning healthcare systems" to address Quality Chasm findings and recommendations.   The vision for value and science driven healthcare was to "catalyze the development of a learning healthcare system – a system in which the processes and systems utilized by the healthcare system enable both the natural delivery of best practices and the real time generation and application of new evidence. The foundational efforts to create consensus standards to improve data quality and fit-for-purpose use identified in section V are critical not only to individual technology assessment but also to healthcare delivery science, implementation science, and learning health care systems (Califf, 2023).

A number of IOM reports were published following the Quality Chasm report and one of the most relevant for HEOR scientists was "The Healthcare Imperative: Lowering Costs and Improving Outcomes" (Institute of Medicine, 2010).   This report focused on six overlapping domains related to health costs:
1. Unnecessary services
2. Services inefficiently delivered
3. Prices that are too high
4. Excess administrative costs
5. Missed prevention opportunities
6. Medical fraud

The six aims from the Quality Chasm report and the six domains from the Lowering Costs and Improving Outcomes report are all areas of potential opportunity for HEOR research, with the possible exception of medical fraud.   The domain of "prices that are too high" has been the "sweet spot" for HEOR scientists who use cost effectiveness to assess the value of pharmaceuticals and medical devices but most of the other domains have also had research conducted by HEOR scientists and presented at ISPOR meetings. The report also identified factors that drive expenditure growth including 1) scientific uncertainty, 2) perverse economic and practice incentives, 3) system fragmentation, 4) lack of trustworthy, understandable sources of information for patients on cost, quality, outcomes, and value, 5) changes in the

population's health status, 6) lack of patient engagement in decisions and 7) under-investment in population health. We would note that both scientific uncertainty and lack of trustworthy and understandable sources of information highlight the need for consensus standards for RWD and RWE. Readers are referred to the IOM reports for more detailed information.

These "areas of opportunities" from the IOM work have more recently spawned the development of new emerging scientific disciplines, including Implementation Science and Healthcare Delivery Science. These disciplines are important for transforming healthcare and will continue to develop with or without ISPOR engagement. Some academic medical centers (Dartmouth University, Cedars-Sinai, Boston University, University of Washington, University of California San Francisco, Johns Hopkins, and Loyola University Chicago) have developed degree programs and there are scientific meetings and other forums. Academic degree programs combine elements of implementation science, healthcare delivery science, economics, and informatics.

Implementation Science was not explicitly addressed by IOM Quality Chasm work, but it was recognized that generating relevant scientific evidence, while necessary, was not sufficient to improve outcomes or lower costs. The scientific evidence had to be implemented into clinical practice and used in healthcare decisions. This important step requires influencing patient and provider behavior through the use of positive incentives, loss aversion disincentives (Prospect theory), or both. The science around implementation directly addresses the challenge of getting scientific evidence into practice … and eliminating healthcare practices when the evidence does not support it.   This work is critical to improve patient outcomes and lower costs*.*

Healthcare Delivery Science addresses how patient outcomes and quality of care can be improved and how costs can be lowered by closely examining every step in the care delivery pathway for inefficiencies, healthcare practices that don't meet quality standards or clinical practice guidelines, and, more generally, lack of evidence-based decision-making. Components of healthcare delivery science such as system redesign have been addressed in the IOM reports, the point here is that, like Implementation Science, Healthcare Delivery Science is an emerging new discipline and research field of its own.

Proposed areas of opportunity for HEOR related research

As previously described, we used the Translational Research Roadmap framework described above to categorize potential opportunities for future HEOR and ISPOR focus. There are many opportunities within the T2, T3, and T4 Roadmap that are well suited to HEOR scientists.

Scientific programming in these areas could also increase ISPOR membership and partnership opportunities from related disciplines that have not historically focused their research on value assessment. Additionally, ISPOR members and HEOR scientists who have traditionally focused their work on value assessment could potentially gain more credibility in their work by also demonstrating expertise in these adjacent areas such as improving quality of care, eliminating waste, increasing efficiency, and increasing the use of scientific evidence in clinical decision making, among other areas described above. These areas of healthcare delivery are of great importance to senior healthcare leaders, including C-Suite executives.

ROADMAP T2 OPPORTUNITIES

Historically most HEOR research has fit within the T2 category, including clinical and economic value assessment of new treatments, comparative effectiveness research, and other areas related to generating evidence on clinical effectiveness. This work is described in detail in Section IV, including potential areas for improvement, and will not be covered here.

ROADMAP T3 OPPORTUNITIES: Improving patient outcomes, lowering costs, improving quality of care, implementation of effective interventions, healthcare delivery redesign, and scaling effective programs.

T3 activities address the "how" of getting from T2-generated clinical and economic value evidence to high-quality, efficient, effective patient care, and involve both implementation and health care delivery science. As previously described, there's been a long history of HEOR work in the T3 areas by HEOR scientists, but it hasn't been a priority for either the discipline as a whole or ISPOR. This is an important opportunity for ISPOR to facilitate the expansion of HEOR's "scope of work", especially since our historic focus on value assessment of pharmaceutical and device products represent a relatively small proportion of healthcare expenditures. Put simply, there is more opportunity – and more "bang for the buck" – if ISPOR is able to shift the focus of HEOR to those areas that account for a larger percentage of healthcare expenditures.

Programs designed to improve quality of care and lower costs are driven by measurement of, and accountability for specific quality metrics that are focused on specific aspects of managing a disease. However, in priority, high-cost health conditions it is sometimes necessary to manage all aspects of patient care including care coordination across systems and providers and coordination of medical resources. This practice has been referred to by many names including "disease management" and "population health management." A critical distinction between disease management and other approaches to traditional medical care is a shift in

focus from treating patients during discrete episodes of care to the provision of high-quality care across the continuum (Ellrodt 1997). This approach gives the opportunity to focus not only on individual technologies but on the entire patient journey, and address issues associated with the main cost drivers including hospital care, personal healthcare and physician services, (Keehan 2023) with the aim of reducing the inefficiencies of the system and improving the health of individuals and populations. This population-based approach to healthcare matches the interdisciplinary nature of HEOR and is consistent with T3 activities based on measurement and accountability for healthcare quality and costs.

ROADMAP T4 OPPORTUNITIES: Population Health, Public Health, and Disease Prevention programs

Following the 2008 publication of the 3Ts Roadmap, many believed that the framework didn't adequately address the public health component of health system redesign. The need for system redesign and capacity building for public health programs is even more apparent following the COVID pandemic. Public Health is now considered the fourth translation step, or T4 (Khoury 2010). The distinction between population health and quality improvement programs between the T3 and T4 categories is nuanced but T4 programs are typically funded by regional and national government agencies and address public health priorities not otherwise covered in T3 programs.

Public Health is defined as "the science and art of preventing disease, prolonging life and promoting health through the organized efforts and informed choices of society, organizations, public and private, communities and individuals" (Winslow 1920). Public health aims are achieved by promoting healthy lifestyles, disease and injury prevention, and detecting, preventing, and responding to infectious diseases. Even though there are some individual technologies such as vaccinations that undergo value assessment and appraisal, public health is more broadly focused on the population level. This scenario represents a challenge and a potential opportunity for HEOR. The work involves making informed choices about how best to spend finite public health resources, quantification of the anticipated impact of an intervention, its cost, the associated opportunity cost, and the possible effect on inequalities. Long-term health impacts, wider societal costs and consequences, impact on inequalities, multicomponent interventions, and interactions within complex non-health sector systems need to be included and correctly assessed to provide useful and reliable information for decision makers (Briggs, 2016). One example of the breadth of public health programs is the county health rankings model used in the U.S. by state health department.   Of note, the impact of "clinical care" is relatively small compared to health behaviors, social and economic factors, and the patient's physical environment. Also of note, health outcomes may be impacted by factors outside of

the traditional healthcare budget, for example, social services and housing.   Global warming
and its consequences such as wildfires and record-breaking high temperatures also have a
health impact on morbidity and mortality.   Crossing budgetary boundaries introduces
challenging complexity.   See Figure 6 below.
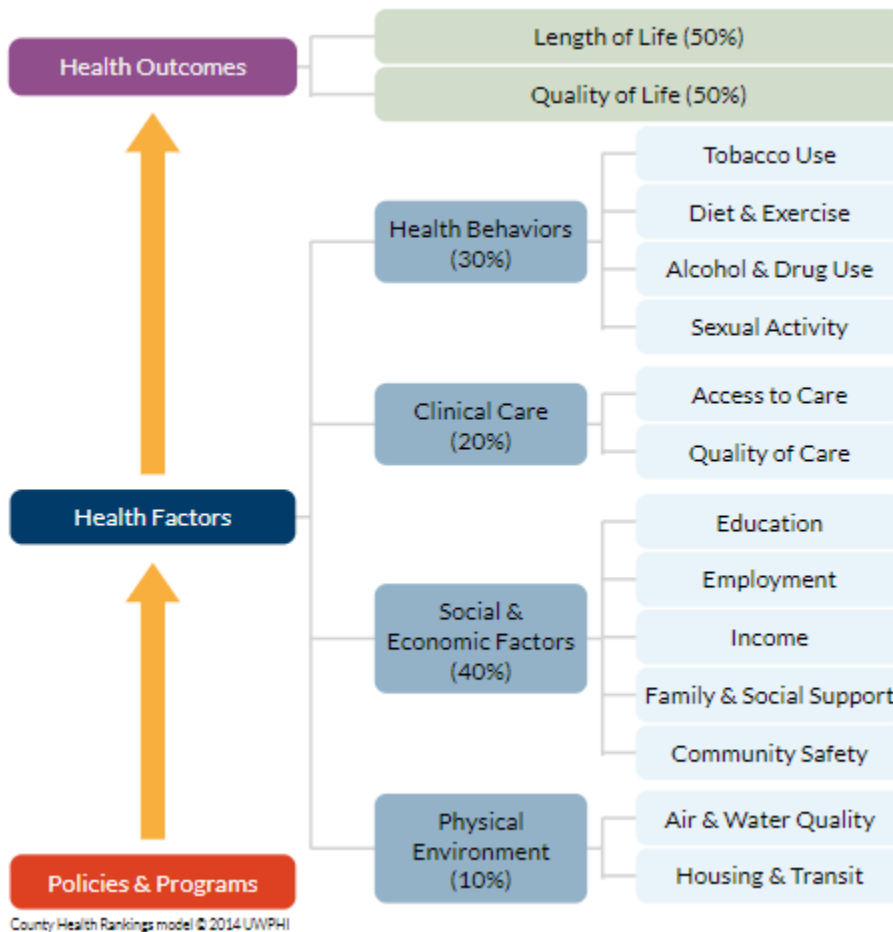
Figure 6. Health Factors Related to Health Outcomes
Source: www.countyhealthrankings.org

Modelling approaches frequently used in health technology assessment, e.g., Markov models,
lack public health context and are not indicated for public health intervention assessment.
More sophisticated modeling, such as complex system models, that can capture the complexity
of public health intervention have been discussed in the literature and further work is needed
to make them a valuable tool for decision makers (Breeze, 2023). One of the main challenges in
public health modelling is balancing transparency and parsimony with complexity; when
developing such models is crucial for model results to be readily interpreted and used by
decision makers.

Section summary

There are many opportunities for HEOR and ISPOR to expand its focus beyond product-level health technology assessment.   We summarize these opportunities as follows:

Opportunity 5: Engage in research and educational content that addresses the largest areas of healthcare expenditures, including hospital care and physician services.

- Hospital care and physician services comprise the largest categories of healthcare expenditures and have the greatest potential to improve patient outcomes and lower healthcare costs.   Specific areas of focus in healthcare delivery could include safety, effectiveness, patient-centeredness, timeliness, efficiency, and equity (IOM 2001).   In the area of efficiency alone, HEOR science could address unnecessary healthcare services, inefficiently delivered healthcare services, high prices (beyond drugs and devices), excessive administrative costs, and missed preventive opportunities.   The emerging scientific disciplines that more broadly address T3 translational research opportunities are Implementation Science and Healthcare Delivery Science. These emerging disciplines provide ISPOR partnership opportunities and educational content opportunities.

Opportunity 6: Engage in research and educational content that increases the use of scientific HEOR evidence in clinical practice guidelines and quality of care measures.

- Scientific evidence is used by quality organizations to develop quality of care metrics and by professional associations to develop clinical practice guidelines.   The adoption validated quality measures and clinical practice guidelines could be one way to assess the use of scientific evidence and, where opportunities for improvement are identified, could lead to implementation science-based interventions aimed at improving their adoption. There is also a need to continue to assess how scientific evidence on the "value" of products and services is used and where opportunities exist for improvement.

Opportunity 7: Better understand factors that drive expenditure growth and develop recommendations to address them.

- The IOM (IOM 2001) identified seven factors that drive expenditure growth: 1) scientific uncertainty, 2) perverse economic and practice incentives, 3) system fragmentation, 4) lack of trustworthy, understandable sources of information for patients on cost, quality of care, outcomes, and value 5) changes in the populations health status, 6) lack of patient engagement in decisions, and 7) under-investment in population health.   These

are all potential opportunities for HEOR, but clinical and economic uncertainty is an area that should be high priority (see section V).

Opportunity 8: Adapt HEOR methods to population-based applications that cover all healthcare delivery in a specific high priority, costly diseases.

- Coordination and evaluation of medical resources for all patients with a specific disease provides an opportunity to identify and address the key cost drivers, including hospital care and physician services. This approach could allow HEOR to have a greater impact on improving patient outcomes and lowering costs.

Opportunity 9: Apply HEOR science to public health programs that address public health interventions on the clinical aspects of healthcare as well as broader issues of health behaviors, social and economic factors, and physical environment.

- Public health programs focus on many important factors that impact health but that are not typically addressed in our healthcare delivery systems and contribute to improving "whole health".   Some of these factors may fall outside of traditional healthcare budgets and pose a challenge for funding.   For example, homelessness results in excessive use of emergency departments as a coping and survival mechanism but housing is not part of healthcare budgets. Public health programs attempt to address these issues in creative ways and we believe there are opportunities for HEOR.

Taken together, pursuing these opportunities can contribute to improving the affordability and economic sustainability of health care in general. While these broader concerns are the result of a myriad of factors, HEOR science has the potential to drive important, value-driven changes in health care delivery and cost.

There may also be risks of ISPOR investing in new areas without a significant return on investment.   We look forward to a more in-depth discussion about which if any of these potential opportunities should be prioritized.

VII. Summary and conclusion

It is critical for the field of HEOR to anticipate the needs of a changing healthcare environment. Given burgeoning scientific capabilities and increasing demands for healthcare globally – yet significantly constrained resources to meet those demands – the importance of informing healthcare decision making to improve health outcomes efficiently and equitably has never

been greater. While HEOR has made substantial contributions in the last 50 years, a further and more nuanced articulation of its opportunities to contribute meaningfully in the future is timely.

Overcoming barriers that have impeded the wider and more impactful use of HEOR evidence is a crucial first step. A targeted literature review identified five types of barriers:

1. Information not relevant or appropriate for the audience;
2. Needed information not available at the time of decision making;
3. Complex information not transparent and not trusted by the decision makers;
4. Lack of training in use of HEOR at the decision-maker level; and
5. System or structural conditions not conducive to HEOR use.

Addressing the first three of these barriers will require a better understanding and anticipation of the needs of specific decision makers - payers, physicians, or patients – and dedication to generating and tailoring HEOR evidence to be useful to them when they need it. Among other things, this means greater attention to validation of the decision analytic models' predictions of long-term outcomes using RWD, as well as identifying better methods for answering the question that individual patients are interested in … "What is the best drug (most effective, safest, etc.) for me?" Continued, improved educational outreach can gradually improve decision maker confidence in the information they are receiving. Greater focus on use of HEOR principles in health policy formation can contribute to reducing the structural barriers.

Individual technology assessment for medicines, genetic therapies, and devices has been the *forte* of HEOR to date and many opportunities, including the growing area of digital health care, exist to enhance what it offers there. These can be summarized as follows: promoting consensus about what constitutes fit-for-purpose RWD and RWE; generation of more complete and relevant HEOR information for use at the time a product is introduced to the market; more targeted generation of HEOR information for use at other parts of the product life cycle; and more focus on the needs of developing countries for applicable HEOR evidence, particularly in the post-patent period.

HEOR also has great relevance beyond individual technology assessment, supported by work earlier this century by the Institute of Medicine in a "Translational Roadmap" that identified six aims and six domains for a "21st-Century Healthcare System" which relate to the efficiency of health care services in practice. HEOR has significant opportunities to contribute here by extending its core methods (modeling and economic evaluation, patient-centered research, RWE), along with healthcare delivery science and implementation sciences, to improve disease

management, public health, and "whole health". Together they can support the development of a learning healthcare system that is structured to use new information more readily, as well as to improve the affordability and sustainability of health care in general.

Opportunities for the enhancement and evolution of HEOR abound. Some involve greater focus on aspects of work already familiar to HEOR researchers in order to increase the usefulness of HEOR evidence to key stakeholders. Others involve applying HEOR principles to domains of health services research that have received less attention from HEOR.   Attention to both data and methods will be necessary for progress in many areas. However, not all opportunities can be pursued equally; the next step for ISPOR is prioritizing among them based on the needs of our patient and health care systems and the interests of our members.

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