

SEPTEMBER/OCTOBER 2023 VOL. 9, NO. 5

# VALUE & OUTCOMES SPOTLIGHT

*A magazine for the global HEOR community.*

## DEVELOPING TOMORROW'S HEOR LEADERS



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# VALUE & OUTCOMES SPOTLIGHT

SEPTEMBER/OCTOBER 2023  
VOL. 9, NO. 5

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## FROM THE EDITOR

# Developing Tomorrow's HEOR Leaders

## Does this sound familiar?

*We have an opening in our health economics and outcomes research (HEOR) department and need to fill that position as soon as possible. We have interviewed a considerable number of candidates but we are unable to identify the right person. So, we are not sure if we should go ahead and hire the best candidate from our current pool with the hope that we can train and develop them for what we need or do we wait and continue to search for the best candidate? If we continue with our search, it may take a long time and we might risk losing the position and be unable to hire anyone.*

Whether in the pharmaceutical industry, consulting, or academia, this situation is more often the dilemma facing hiring managers—all of which are in search of talented individuals with a desirable skill set that allows those hires to be productive and contribute to an organization immediately.

As today's healthcare environment is evolving with new drug targets, innovative drug therapies, new technologies, digital health, artificial intelligence, and robotics, it will become more critical for HEOR professionals to apply new methods, model cost-effectiveness, and measure health outcomes to demonstrate value and impact from various perspectives, including those of providers, payers, patients, and caregivers. It will also be important for those professionals to have the skills to adapt to a hybrid work environment, as we are already seeing many companies incorporate hybrid work into their organizations. Many have embraced this hybrid model as it has allowed them to

**Effective communication and interpersonal skills, leadership, problem-solving, teamwork, critical thinking, collaboration, and time management are personal qualities and traits critical for any successful HEOR professional.**

recruit around the world yielding a more diverse workforce than ever before. This situation has ushered in a new level of training and development focused on cultural competence in support of creating a respectful and inclusive workplace.

To develop tomorrow's HEOR leaders, it is essential to provide them with the necessary skills and knowledge to succeed in the field. Core HEOR skills are usually gained through master's and doctoral degrees offered by

formal academic programs at colleges and universities. Post-doctoral fellowships are also available and offered by pharmaceutical and consulting companies in partnership with academic HEOR programs. These fellowships provide additional HEOR academic training and research, as well as hands-on application of these learnings at the sponsor companies. Additional avenues for obtaining HEOR training are available (eg, HEOR certificate programs, short courses [which are offered by many organizations such as ISPOR], webinars, targeted training by organizations, as well as short-term internships available at many companies).

Along with technical training, essential soft skills are also important for the development of HEOR professionals. For example, effective communication and interpersonal skills, leadership, problem-solving, teamwork, critical thinking, collaboration, and time management are personal qualities and traits critical for any successful HEOR professional. The ISPOR HEOR Competencies Framework highlights the various competencies that professionals need for success in the field of HEOR. These competencies should be incorporated in academic training, as well as continuous development of HEOR professionals.

Mentorship is another valuable tool for both personal and professional development in HEOR. It establishes a collaborative relationship between experienced and new professionals and students, playing a key role in the development of all parties involved. Mentorship builds confidence and character, challenges comfort zones, and creates lasting connections. It helps to establish an independent and productive professional, assists the mentees in establishing clear learning goals and professional relationships, and stimulates the mentees to acquire both theoretical knowledge and practical skills. Good mentorship benefits not only students and new professionals as mentees but also the mentors and institutions that support them. Mentorships also enhance medical and health professions overall by facilitating the process of sharing knowledge between disciplines and generations.

Developing tomorrow's HEOR leaders requires a comprehensive approach that includes education, training, and practical experience. To be successful in the field, HEOR professionals must have a solid foundation in not only HEOR but also epidemiology, biostatistics, and clinical research methodology. They must also be able to communicate effectively with stakeholders, including patients, healthcare providers, payers, and policy makers. By providing aspiring professionals with the necessary skills and knowledge, we can ensure that they are equipped to make informed decisions that improve healthcare outcomes for patients around the world.

As always, I welcome input from our readers. Please feel free to email me at [zeba.m.khan@hotmail.com](mailto:zeba.m.khan@hotmail.com).

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



## FROM THE CEO

## Cultivating Core Competencies in Health Economics and Outcomes Research

Rob Abbott, ISPOR CEO and Executive Director

In 1990, two of the world's leading experts on business strategy, C.K. Prahalad and Gary Hamel, published a book that would have—and continues to have—a significant impact on my thinking about how to create enduring value in an organization. The book was titled, *The Core Competence of the Corporation*, and the central idea was that a company must define, cultivate, and exploit its core competencies to succeed against its competitors. Those competencies are the resources and capabilities that collectively comprise or create strategic advantage. One can think of them as “the collective learning in the organization, especially the capacity to coordinate diverse production skills and integrate streams of technologies.” Microsoft, for example, has cultivated expertise in many expressions of IT that have been difficult for competitors to replicate. This, in turn, has continually reinforced Microsoft's strategic advantage in the market.

**The relevance of core competencies is not limited to business; the theory and practice of cultivating core competencies is every bit as important in the public and not-for-profit sectors.**

The passage of time has only burnished the relevance and impact of the core competence theory. In fact, many of the more popular management books of the past 3 decades—*Good to Great*, *Blue Ocean Strategy*, *Black Box Thinking* and others—owe more than a little debt to the pathbreaking work of Prahalad and Hamel. Equally, the relevance of core competencies is not limited to business; the theory and practice of cultivating core competencies is every bit as important in the public and not-for-profit sectors. All of which brings me to the theme of this month's issue of *Value and Outcomes Spotlight*, and the opportunity it affords to consider the [Health Economics and Outcomes Research \(HEOR\) Competencies Framework™ initiative](#).

ISPOR's [Institutional Council](#) and [Faculty Advisor Council](#) have been actively leading an effort for several years now to articulate a core competencies framework for HEOR. The overarching objectives of their work has been to define:

- Competencies that professionals need for success in the field of HEOR;
- Competency gaps that are often seen in candidates and employees; and
- Training and education gaps that need to be addressed.

ISPOR published its Health Economics and Outcomes Research (HEOR) Competencies Framework™ in the September 2020

issue of *Value in Health*.

The report, “[Competencies for Professionals in Health Economics and Outcomes Research: The ISPOR Health Economics and Outcomes Research Competencies Framework](#),” was the

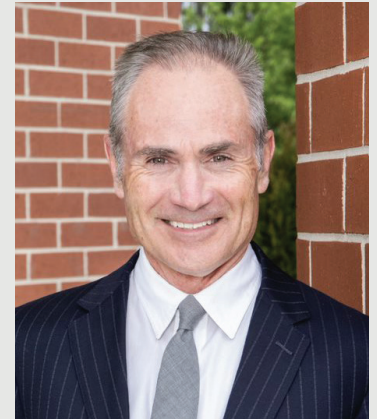
first large-scale effort to

formally identify competencies from within the HEOR field. These competencies can serve as a tool to guide academic curricula, fellowships, and continuing education programs, as well as the assessment of job candidates for HEOR career opportunities. The framework can also provide HEOR professionals with a valuable resource to help guide their professional development. The first tranche of core competencies is highlighted on the ISPOR website (<https://www.ispor.org/strategic-initiatives/more/heor-competencies-framework>) and discussed more fully in several of the papers contained in this issue of *Value & Outcomes Spotlight*. They are:

- Business management
- Economic evaluation
- Study approaches
- Clinical outcomes
- Career development
- Health policy and regulatory affairs
- Patient-centered research
- Health technology assessment
- Organizational practices
- Communications and influence
- Health service delivery and process of care
- Methodological and statistical research
- Epidemiology and public health

What is striking about this list of competencies is the breadth—as well as the depth—of experience and expertise that is needed to truly bring value to healthcare decision making. This will only become more urgent as our profession seeks to make a meaningful contribution to the big, complex health challenges of our time: affordability, the impact of digitalization on health, and the growing interest in “whole” health.

I am grateful to the efforts of the many ISPOR members who have contributed to the HEOR Competencies Framework™ initiative and pledge my support as your CEO & Executive Director to support continued development and refinement of the Framework, and to communicate its value to anyone interested in improving healthcare decisions.



## ISPOR NEWS

## Real-World Evidence: From Frameworks to Practice

### Summary of the May 2023 ISPOR/ISPE/Duke-Margolis Summit

Richard J. Willke, PhD, Chief Science Officer Emeritus, ISPOR, Lawrenceville, NJ, USA



#### Introduction

Where does the credibility of real-world evidence (RWE) currently stand in regulatory and health technology assessment (HTA) decision making? What is the most recent thinking about real-world data (RWD) quality, fit-for-purpose use, and transparency criteria? What are we learning from ongoing efforts and actual cases of RWE in these areas? These were the key questions addressed during the ISPOR/ISPE/Duke-Margolis RWE Summit, entitled, “Real World Evidence: From Frameworks to Practice,” held on May 7, 2023 in Boston, Massachusetts.

#### What is the most recent thinking about real-world data quality, fit-for-purpose use, and transparency criteria?

This Summit comprised four 1-hour sessions on data quality, fit-for-purpose use, study transparency, and case studies, respectively (see Figure for full session titles and speaker names). Speakers included representatives from regulatory bodies, HTA agencies, academia, industry, consulting/data research companies, and the sponsoring organizations—a healthy balance of stakeholder interest and activity in RWE. An engaged, sold-out audience ensured vigorous question and answer periods. Each session’s discussion is summarized below. The slides from the session can be found [here](#).

#### From Data Quality to Qualities

The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have each recently created guidance on RWE data quality, among their other RWE-related guidances. The FDA defined 2 major criteria for quality—relevance and reliability—where *relevance* includes the availability of key data elements and representative patients for the study, while *reliability* includes accuracy, completeness, provenance, and traceability. The EMA considered reliability and relevance as well as extensiveness, coherence, and timeliness, as aspects of data quality. While their respective definitions of these criteria have much in common, they are not identical and thus there is potential for differing standards. The International Coalition of Medicines Regulatory Authorities has called for harmonization of RWE terminologies and convergence of guidance and best practices across countries. In general, reliability is seen as an intrinsic aspect of the data’s quality, while relevance refers to the data’s applicability to the particular question at hand and speaks to its being “fit-for-purpose” for that question.

The major threat to the reliability of RWE is its potential for biases (eg, selection, information, and confounding biases). To

#### AGENDA

Welcome: **Rob Abbott**; ISPOR CEO & Executive Director

#### SESSION 1: From Data Quality to Qualities

Moderator: **Rachele Hendricks-Sturupp, DHSc, MSc, MA**; Duke-Margolis Center for Health Policy, Washington, DC, USA

Speakers: **Andre Araujo, PhD**; GSK, Kennett Square, PA, USA  
**Jaclyn L. Bosco, PhD, MPH**; IQVIA, Cambridge, MA, USA

**Sebastian Schneeweiss, MD, ScD**; Harvard Medical School; Brigham and Women’s Hospital, Boston, MA, USA

#### SESSION 2: Considering Data Qualities in Determining Fit-for-Purpose: Can We Converge on an Approach?

Moderator: **Marc Berger, MD**; Marc L. Berger, LLC, New York, NY, USA

Speakers: **John Concato, MD, MS, MPH**; US Food and Drug Administration, Silver Spring, MD, USA

**Gracy Crane, PhD**; Roche Products Limited, Welwyn, HRT, United Kingdom

**Laurie Lambert, PhD**; Canadian Agency for Drugs and Technologies in Health, Ottawa, ON, Canada

**Daniel Leaver Morales**; EMA, Amsterdam, The Netherlands

#### SESSION 3: Transparency in RWE: Ensuring Credibility and Confidence

Moderator: **Richard Willke, PhD**; ISPOR, Lawrenceville, NJ, USA

Speakers: **Adam Aten, MPH, MSc**; Duke-Margolis Center for Health Policy, Bethesda, MD, USA

**C. Daniel Mullins, PhD**; University of Maryland School of Pharmacy, Baltimore, MD, USA

**Shirley Wang, PhD, MSc**; Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA

#### SESSION 4: Navigating the RWE Landscape—Successes, Struggles, and the Path Forward

Moderator: **Nancy Dreyer, MPH, PhD**; IQVIA Real World Solutions, Newton, MA, USA

Speakers: **Stephen Duffield, PhD, MD**; NICE, Liverpool, United Kingdom

**Wim Goettsch, PhD**; National Health Care Institute; Utrecht University, Division of Pharmacoepidemiology and Clinical Pharmacology, Diemen, The Netherlands

**Ashley Jaksa, MPH**; Aetion, Inc, Boston, MA, USA

**Tae Hyun Jung, PhD**; Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, USA

Closing Remarks: **Richard Willke, PhD**; ISPOR, Lawrenceville, NJ, USA

assess and quantify the potential for bias, the measurement characteristics of the data (such as missingness, sensitivity and specificity of coding, or accuracy of timing of event onset) must be analyzed and documented. The [FDA Sentinel Initiative](#) has created a structured “data-adaptive review cycle” for electronic health records to assess whether measurement performance is adequate and to apply corrective measures when needed and possible. Using Sentinel data, they demonstrated that high-quality RWD—combined with target trial emulation study designs—can regularly replicate randomized clinical trial (RCT) results.

From the industry sponsor side, it is critical to have clear criteria for, and documentation of, data quality to satisfy regulatory requirements. As part of a larger collaborative effort to enable the use of RWE, the Transcelerate Initiative produced its draft, “[Real-World Data Overview: RWD Audit Readiness](#),” in early 2023 for public review. It includes definitions and suggested documentation for data relevance, accrual, provenance, completeness, and accuracy. At the time of the Summit, the draft was under revision based on public comments.

### The major threat to the reliability of real-world evidence is its potential for biases (eg, selection, information, and confounding biases).

The [RWE Alliance](#) is a coalition of RWD and analytics organizations with a common interest in harnessing the power of RWE to inform regulatory decision making to improve patients’ lives. It has been trying to address some challenges created by recent regulatory guidances for RWE. These challenges include access to patient-level source data (eg, privacy concerns), conversion of RWD to a supported standard (which may sacrifice some granularity), data quality assessment and examples thereof (more are needed), and clarification of data collection and analysis expectations. To assess the role of data source variability, a pilot study was conducted where each data organization estimated, using its own data, the treatment effect on survival of a given oncologic product. Estimated treatment effects varied considerably, leading to some recommendations on data quality assessment: (a) develop a template, (b) use a quantitative approach, (c) use careful evaluation by experts with deep knowledge of the data, and (d) use quality indicators for the data.

Audience comments during the session related to who bears responsibility for data quality, the particular importance of high-quality data for exposure and outcomes, the need to establish higher RWD collection standards, and the need for standards for non-Western data.

#### Considering Data Qualities in Determining Fit-for-Purpose: Can We Converge on an Approach?

While some data quality aspects may be largely inherent in the data, judging whether data are fit-for-purpose combines the data’s intrinsic quality, particularly reliability, with the specific question being addressed (ie, its relevance). This session sought to consider the question of whether standards for

fit-for-purpose used can be harmonized across agencies and countries. Following brief presentations, several questions were posed to the panel.

FDA considerations when judging RWE, as stated in their [2018 guidance](#), can be characterized by 3 “swim lanes”: (1) whether the RWD are fit for use; (2) whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question; and (3) whether the study conduct meets FDA regulatory requirements. To assess fit-for-purpose use, relevance and reliability must be assessed. RWD-based study designs can potentially yield evidence that meets the statutory standard for substantial evidence (there is not a different standard for RCT vs RWE results), although the degree of certainty supporting an FDA conclusion about substantial evidence of effectiveness may differ depending on the clinical circumstances (eg, disease severity, unmet medical need). Representative problems observed by FDA with RWE relate to 3 main factors: (1) real-world data sources, (2) nonrandomized study designs, and (3) conduct of nonrandomized studies.

From the EMA’s perspective, the fit-for-purpose standards they apply align well with FDA’s, although they do explicitly identify coherence, extensiveness, and timeliness in their [Data Quality Framework](#) (DQF). More guidance is probably needed in exactly how they will be operationalized; however, some regulatory judgment is needed in what evidence is truly fit-for-purpose. In addition to the DQF, EMA has also produced their [Good Practice Guide for the Use of Real World Metadata](#), which is based on using a metadata catalog developed by ENCePP as one selects data for a given study and provides the needed aspects of the data in the study protocol.

At Canadian Agency for Drugs and Technologies in Health (CADTH), HTA is done not only initially but also later in the product life cycle and considers not only safety and effectiveness but also resource costs as well as patient, societal, and cultural factors. As such, RWD is an important tool, and transparency in the generation and reporting of RWE is critical for their evaluation. CADTH is launching, after public review, guidance for reporting RWE to ensure that regulators and HTA agencies have sufficient information to evaluate a study for its appropriateness of use for decision making, to provide core reporting standards for RWE studies that align with global standards, and to prioritize transparency in reporting while accounting for practical challenges related to RWD and RWE.

From an industry perspective, components of the multifaceted nature of fit-for-purpose RWD result in many “moving parts” that need to work together to enable use of RWD for regulatory and HTA decision making. These include the regulatory or HTA context, filing strategy, clinical context, data sources, methods, and established data standards. The industry “ask” is for convergence on common principles for characterizing data quality for global drug development.

The first question posed to the panelists was: “What is the relationship between the standards for data quality and fitness-for-purpose? Do they not vary with the nature of the regulatory decision?” Briefly, the panelists all replied “yes”—both the

context and the totality of the evidence matter for the regulatory decision. Context includes a judgment about whether the data context (eg, population or clinical setting) is applicable to the decision context. Similarly, the credence given to the RWE may depend on its consistency with, or reason for being different from, other evidence.

The second question was “While the criteria for fitness-for-purpose may be bespoke for a particular regulatory question, doesn’t one consider what has been learned about the ‘operating characteristics’ of particular data sources based on their track record for producing credible RWE?” The answer was again, essentially, “yes.” Past experience with the data does matter for understanding of intrinsic data quality, although data completeness can vary from variable to variable and thus from study to study. In some cases, fitness-for-purpose can be best evaluated by showing the “unfitness” of the data (ie, how certain data imperfections can affect study results). This “unfitness” can sometimes be fed back to the data collectors to improve future data collection.

The third question was, “Data quality and fit-for-purpose standards will likely vary when there exists RCT data related to the therapeutic in question as opposed to when standard RCTs are not available for feasible. Does this mean that there are different standards for sufficient (substantial) evidence?” As addressed earlier in the session, substantial evidence standards should stay the same, since they are about the fundamentals of the data and research question. Nevertheless, early interaction between sponsors and regulators about RWD study plans can help with specific aspects there. In addition, it may depend on the totality of evidence since the complementarity of RWE and RCT evidence may affect the decision.

Questions from the audience brought out several additional points:

- Benchmarking of data quality standards would be most useful and could help data curators report on their processes; documentation of dataset quality needs much improvement.
- Experience with some regulatory committees (eg, NICE) indicates that RWD has rarely been used for comparative effectiveness and also that the opinions of 1 or 2 clinical experts can greatly affect decisions about data quality and credibility.
- Transparency of the research process is becoming quite important to decision makers; conversely, transparency of the decision-making process is important to stakeholders but is often still lacking—more case studies are needed.
- Completeness (lack of missingness) of data is often critical but standards there would be most helpful.

### Transparency in RWE: Ensuring Credibility and Confidence

In the first 2 sessions, the importance of study transparency was mentioned several times. The third session expanded on efforts to improve transparency via protocol registration, use of protocol templates and master protocols, and considerations for publication.

Preregistration of RWE study protocols improves confidence that the results were not based on a data-mining exercise. In recent years, registration of RWD/observational studies in the best-known protocol registry, [clinicaltrials.gov](https://clinicaltrials.gov), has increased significantly, although it is still structured better for prospective studies. The [EU PAS Register](#), originally created by EMA for post-authorization studies in Europe, is also an option for registering safety or comparative effectiveness studies using RWD. In the last few years, the [RWE Registry](#) was created by the ISPOR/ISPE/Duke-Margolis/NPC Transparency Initiative. Hosted by the Center for Open Science, it is specifically designed for efficient registration (ie, half as many questions as [clinicaltrials.gov](https://clinicaltrials.gov)) of RWD cohort, case-control, or other retrospective study designs, and has a “lockbox” option to maintain confidentiality of ongoing studies. All the databases are searchable so that they can be used for systematic or other types of literature reviews.

**Preregistration of real-world evidence study protocols improves confidence that the results were not based on a data-mining exercise.... Journal editors are starting to seriously consider the need for preregistration of RWD study protocols.**

The HARPER ([HARmonized Protocol to Enhance Reproducibility](#)) protocol template, created by a recent ISPE-ISPOR Special Task Force, provides a structure for creating and documenting elements of a RWD study protocol. It is intended to promote transparency and reproducibility of noninterventional study protocols by academics, companies, and regulators. It is compatible with the legal format and content of the [GVP Module VIII](#) on PASS and can already be used in PASS protocols without change of structure. Several pilot initiatives using HARPER, as well as training in its use, are in progress.

There is also an ongoing initiative led by Duke-Margolis to create an RWE Master Protocol. An RWE Master Protocol design is meant to align research questions with appropriate methods and data sources to facilitate consistent implementation and replication. A linchpin to implementing RWE master protocols is understanding data requirements for the study, including the translation of study questions into RWD, data requirements and programming specifications, and data quality considerations. A white paper based on the work of this initiative is expected soon.

From a journal's perspective, editors want both transparency and validity in the manuscripts they review. Of the two, validity is likely more important but good transparency is important for determining validity, and a prespecified protocol helps ensure that the researchers did what they originally intended to do. Journal editors are starting to seriously consider the need for preregistration of RWD study protocols but have not reached consensus yet. More journals are now using “badging” (ie, small icons accompanying article titles) to indicate study characteristics like protocol registration. Incorporation of a registration number into reporting checklists like [PRISMA](#) or [CHEERS](#) would help reviewers see it as an important study element. *Value in Health*



is moving towards having expedited review for preregistered studies as an incentive for doing so.

Audience Q&A emphasized the need to broaden the discussion about these transparency tools to more audiences, especially those who may use RWD less regularly—in academia, industry, clinical practice, journalism, etc. Incentives and ease of use will be keys to their becoming normal practice.

### **Navigating the RWE Landscape—Successes, Struggles, and the Path Forward**

An important complement to guidances and tools is experience with how they are implemented in actual practice and decision making. This session provided details on a number of specific cases involving RWE in regulatory and HTA decisions.

In the United States, while RWE has been used by FDA as *supplementary* evidence of efficacy in a few cases, the first time RWE was used as *primary* evidence of efficacy was in 2021, for a new indication of tacrolimus for prevention of organ rejection in lung transplants. It relied on data from a non-interventional (observational) treatment arm, where tacrolimus was used off-label, compared to historical controls, with both arms drawn from the Scientific Registry of Transplant Recipients data on all lung transplants in the United States during 1999–2017. The primary endpoint was graft failure or all-cause mortality at 1 year. There were some issues with the study data and analysis (eg, relating to the choice of index date and some missing data) but they were resolved by discussions between the agency and the sponsor. Lessons learned relate to the topics discussed at this Summit—ensuring data reliability and relevance, prespecification of the study protocol, and robust scientific rationale for study and analysis choices. While the decision shows that RWD/RWE brings opportunities, there have also been some “failures” at FDA—one where it was decided that the RWE for an external control did not match clinical data for inclusion/exclusion criteria and standard of care, and one where RWE was not allowed to be added for effectiveness for lack of relevance and reliability. As an additional point, it was noted that FDA is exploring more use of machine learning and natural language processing for safety surveillance.

At NICE, a current focus is implementing the [RWE Framework](#) they published in 2022. One case related a review of mobocertinib for *EGFR* exon 20 insertion-positive non-small cell lung cancer after platinum chemotherapy. Treatment evidence came from phase I and phase II single-arm trials, with external control arms that used US and German RWD and adjusted indirect treatment comparisons. There were several review issues related to data provenance, effects of missing data, use of pooling, and relevance of case-mix adjustments. After a company response with more data provenance information and several scenario/sensitivity analyses, a positive decision was made; however, NICE felt uncertainty could have been reduced more. As at FDA, there have been significant challenges—both for HTA and clinical purposes—with use of RWE, ranging from gaps in the NICE RWE Framework, to data access, to need for organizational upskilling. In addressing these challenges, NICE is committed to stewarding RWE across the evidence life cycle.

As discussed earlier, an important factor in the success of RWE studies is ensuring that the data are of high quality and fit-for-purpose. To that end, Zorginstituut Nederland (ZIN) is working to provide national guidance on disease-specific patient registries to enable the production of high-quality comparative effectiveness and cost-effectiveness studies. This effort involves establishing minimal data sets with involvement of all stakeholders, using a new tool (REQUEST) to assess the data quality and transparency of the patient registries, as well as piloting the HARPER template to help define the research question. Lessons learned include the value of REQUEST in helping registry owners better document their data characteristics; the value of HARPER tool's graphical representation of exposure-based cohort entry for establishing index dates; and the difficulty many registries have linking with electronic health records.

**In a growing number of cases across countries, data quality has been judged good enough to support regulatory/HTA decisions about drug efficacy or effectiveness.**

External control arms (ECAs) are presently the primary use of RWE for regulatory decisions. A recent study by [Jaska et al](#) reviewed decisions made by 3 regulators and 5 HTA agencies on 7 drug applications using ECAs. It tracked the positive and negative comments on specific aspects of RWE data analyses, finding variability and sometimes disagreement across agencies. The most prevalent critiques related to generalizability/relevance (eg, inconsistency of the standard of care in the ECA over time) and mitigation of confounding, which are well-known issues but may lessen as data quality and study designs improve; variability across agencies should improve as more of them produce their own RWE guidances.

Looking ahead, there are many opportunities for postlaunch use of RWE to address evidence gaps and uncertainties, but key questions remain. Who is going to review evidence? At what time points? Based on what regulations? How are evidence gaps prioritized? Who bears the burden of evidence generation? Will data be transferable across countries? Multistakeholder collaborations, such as a current one between Health Canada and Aetion, may be a path forward to help answer some of these questions.

Subsequent discussion highlighted several more points. First, RWD quality is still seen as a major issue by many HTA agencies. Efforts to improve data quality, especially its relevance, are being pursued in several ways, such as collection of new patient endpoints via wearables, linkage of administrative data with community-based data collection from individuals, and longitudinal linkage of data across insurers to collect long-term outcomes data. The importance of transparency from all concerned was also reemphasized—both clear explication of the study design and process by sponsors/researchers, as well as more explicit statements by reviewers about the merits or issues

driving decisions about submissions—along with the desirability of a repository of regulatory/HTA decisions with key criteria identified.

### Summary

Collectively the 4 sessions of the Summit provided many key insights into the questions posed at the beginning of this article. Data quality for RWD has been defined by several agencies and focuses on the general aspects of reliability and relevance. In a growing number of cases across countries, data quality has been judged good enough to support regulatory/HTA decisions about drug efficacy or effectiveness. However, there is considerable room for improvement. For reliability, more consistent attention to the measurement characteristics and curation of the data, as well as structured documentation of both, is needed. Questions about who has responsibility for data quality must be resolved and multistakeholder efforts are needed there. Relevance of the data to the clinical context and the population are critical for their use in decision making for specific indications. To make study results credible, proper study designs to deal with selection bias and confounding, transparency of study process, and addressing uncertainty (to the extent possible) via scenario

and sensitivity analysis are all important. In the end, decision making may also be influenced by factors like the totality of the evidence, unmet medical need, and magnitude of treatment effect relative to price. As data reliability is improved and experience with use of RWE accumulates, one can anticipate its increasingly greater use for both initial regulatory decisions and subsequent reevaluations during the product life cycle.

**Acknowledgments:** This article directly incorporates a number of points from the speakers' slides as well as their remarks during the sessions; to simplify the exposition, quotations marks and attributions are not used, but readers are encouraged to refer to the linked slides and recording as original sources. The assistance of the Program Committee in creating the agenda for this Summit (Marc Berger, William Crown, Nancy Dreyer, Shirley Wang, Rachele Hendricks-Sturup, Sebastian Schneeweis, David van Brunt, Gracy Crane, Lucinda Orsini, Massoud Toussi, Adam Aten, Christina Mack), is gratefully acknowledged, as is the work of Kat Bissett, Meredith Kaganovskiy, Paul Wong, and other ISPOR staff members in making all the needed arrangements, as well as Lyn Beamesderfer's help in reviewing this article.

## ISPOR NEWS

## ISPOR 2023: Bringing the HEOR World Together

Christiane Truelove

ISPOR's annual conference, which took place in Boston, Massachusetts in May, drew more than 4500 delegates from 71 countries, hosted more than 450 speakers across 130 sessions, and presented 180+ hours of content. The main themes at the conference were **affordability and innovation**, **real-world evidence**, and **artificial intelligence in healthcare**. In real-world evidence, discussions focused on reproducibility, transparency, governance, and data quality, especially by healthcare regulators and policy makers.

The highlights and commentary on the content and activities of ISPOR 2023 events in Boston are summarized here and are also available to all ISPOR members via the [ISPOR 2023 Key Insights Session](#).

### Affordability and Implications of the Inflation Reduction Act

Samantha Roberts, DPhil, MBA, (National Institute of Health and Care Excellence, United Kingdom and conference co-chair), moderated the first plenary session at the conference, "[Global Focus on Affordability and Inward Investment: What Does It Mean for HEOR?](#)" Roberts was joined by the following panelists: John M. O'Brien, PharmD, MPH (National Pharmaceutical Council); Michael Drummond, MCom, DPhil (University of York); and Meena Seshamani, MD, PhD (Centers for Medicare & Medicaid Services).

Besides discussing value pricing and affordability across countries, the panelists took a deep dive into the provisions of the Inflation Reduction Act, addressing its effects on consumer out-of-pocket spending and factors relating to value that may be brought into Medicare price negotiations, and how all this may affect incentives for innovation.

Roberts pointed out that health and care systems around the world "are struggling with affordability of medicines. Whether we like it or not, drug costs are a big part of that affordability issue." She predicts that changes are coming. "Governments are going to introduce policies to try to tackle this and we, as an HEOR community, can't sit on the sidelines and criticize those policies. We need to be part of the effective implementation of these policies and play an active role in considering the intended and unintended consequences of their implementation. The call is for this community to engage with governments and payers—curiously, creatively—to find new approaches and solutions together."

Laura T. Pizzi, RPh, PharmD, MPH, chief science officer at ISPOR, characterizes the Inflation Reduction Act as "probably the number one topic of this meeting," as the act has pushed HEOR into mainstream conversations. "This is a pivotal moment for our science," Pizzi said.



This conversation on affordability will center on value. "Value is what we do in HEOR. We specialize in the science of measuring it. We definitely want the conversation to be about value," Pizzi said.

Currently, those making value determinations about new drugs are dealing with a limited amount of data. Because of this, the Inflation Reduction Act does not provide for drug price negotiation until 9 years post launch. "By 9 years out, we need to strive as a field to have sufficient evidence to inform that negotiation process," Pizzi said. "That is a major, major change in how the industry operates and how our field has operated with decision making. It's really exciting and presents so much opportunity for us."

### Advancements in Real-World Evidence

William Crown, PhD, distinguished research scientist, Brandeis University, United States and [ISPOR 2023 RWE Summit](#) program committee member, commented on the "packed" conference agenda. For him, one important takeaway was the report out on the US Food and Drug Administration-funded [RCT-DUPLICATE study](#), which examined 32 clinical trial emulations attempting to mimic the inclusion-exclusion criteria of trials, the endpoints, and the treatments that were studied in trials with observational data.

"The degree of agreement between these observational studies and the randomized trials was really pretty impressive," Crown said. "It was over 90%. This suggests that we're always going to need randomized trials, especially for studying new treatments where there are no data on them in these observational databases. But it also shows that in cases where we can't do trials (eg, in the middle of a COVID pandemic) where we're trying to figure out what treatments work and what treatments don't, observational studies can allow us to get reliable answers without the time-consuming process of recruiting patients and waiting for outcomes so that we can act more quickly."

Another takeaway from the RCT-DUPLICATE study was around issues of transparency. "It's really important that when these observational studies are being done that people understand that there isn't a cherry-picking of the results," he said, pointing to the guidance released by ISPOR and the International Society for Pharmacoepidemiology (ISPE) in 2022, "[HARmonized Protocol Template to Enhance Reproducibility \(HARPER\)](#)." The guidance came out of an [ISPOR/ISPE joint task force](#) to develop a uniform template to help collect real-world data and conduct real-world evidence studies. The report describes how to design an observational study to get a reliable estimate from it, "because

it's not only the data, but it's also how you design the study," Crown said. "When you have good data and good design, you can get really close to the same results you would have gotten had you done a time-consuming and expensive clinical trial."

### Causal Inference and Electronic Health Records

Conference Co-Chair Sebastian Schneeweiss, ScD (Brigham and Women's Hospital) moderated the third plenary, "[Issues and Solutions When Estimating Treatment Effects Using US Electronic Health Record Data](#)," which looked at several issues that arise when performing causal inference studies with electronic health record data and presented potential solutions in each case. Richard Wyss, PhD (Brigham and Women's Hospital) discussed methods for adjusting for confounders and ultra-high dimensional covariant settings. Jeremy Rassen, ScD (Aetion Inc) gave an example of how submitting an active comparator studying design, instead of a no-treatment comparative design, helped reduce bias. Rebecca A. Hubbard, PhD (Hospital of the University of Pennsylvania) talked about informative presence bias in electronic health record data. Janick Georg Weberpals, PhD (Brigham and Women's Hospital) reviewed diagnosing patterns and missing data.

According to Schneeweiss, "The session was driven by the underlying data that become available, and as more and more electronic health record data become available, new methods are developing that make optimal use of these real-world, electronic health records. We have learned a lot about claims data in the past 25 to 30 years. Now, we're in a new era of learning how to analyze electronic health record data and a lot of issues are coming up. As there is quite a bit of heterogeneity in these data, it is important to realize that the way we as physicians practice medicine has direct implications of the data structures and on how we analyze the data. And that needs to be factored into the analytic methods that we are developing."

Pizzi points out that HEOR methods evolved "in an era where we didn't have enough data." The old way of choosing a comparison cohort would be that you would look at patient demographics, you would look at their treatment characteristics, you would look at their disease severity, and you could do a reasonable job matching your treatment in comparison groups that way," Pizzi said. "But with real-world evidence, you still might have some imbalances that exist despite doing that."

### Artificial Intelligence in the Physician's Office

Conference Co-Chair Mitchell Higashi, PhD (GENEDx) moderated the second plenary session, "[AI Wants to Chat With You: Accept or Ignore?](#)" The session featured Blythe Adamson, MD, MPH (Flatiron Health); Jacqueline Shreibati, MD (Google Health); David Sontag, PhD (Massachusetts Institute of Technology); Guillermo A. Cecchi (IBM Research and National Institute of Health's Advancing Medicines Partnerships–Schizophrenia); and Mary Beth Ritchey, PhD, MSPH, BSN (FDA/CDRH/Office of Product Evaluation and Quality/Office of Clinical Evidence and Analysis).

According to Higashi, "The promise of using artificial intelligence and large language models is that we have this vast universe of unstructured data." He estimates that currently, HEOR experts only work with 20% of the available data, which exist primarily as structured claims data and structured physician notes.

"All the data captured on devices (ie, your conversations, often your informal conversations) will capture a lot of situational context, but any data relating to your emotional state and your quality of life are lost to us," Higashi said. "Artificial intelligence and large language models have the potential to structure some of that unstructured data. What that means for us in HEOR is we can do more robust science and improve patient outcomes."

According to Pizzi, one of the main points the panel made was that large language models are now becoming a part of daily life, with ChatGPT bringing them into the mainstream. "There's no question that artificial intelligence is here to change healthcare and will impact HEOR as well," she said. "Where we as a field could have a significant impact is that when we talk about these large language models, we're effectively talking about taking enormous volumes of text or unstructured data and creating standardized data from that. But the question is, once it's standardized, how do you validate it? And we know how to validate measures. We've done it for patient-reported outcomes measures and other types of survey instruments that we use in the field. We have to point our methods now towards the structured data that are emerging from these large language models."



### Knowledge Treasure of Poster Sessions

Additionally, there were more than 2000 research posters presented—most of them now available in the online [ISPOR Presentations Database](#).

Amy Buchanan Hughes took attendees on a poster tour sharing research on the topic of real-world evidence. Some of these posters focused on target trial emulation, the use of real-world data to emulate randomized clinical trials. One presenter shared the results of an emulated target trial using a couple of different methods, yielding "relatively robust" results. According to Hughes, "That was quite reassuring to see that we are applying methods that we've been hearing about throughout the conference in quite high-level ways and quite generalized terms."

Khalid Kamal, PhD, chair and professor of pharmaceutical systems and policy, West Virginia University School of Pharmacy, moderated a poster tour on pricing reimbursements. The presentations included posters on the impact of biosimilars and how they can reduce biologic or the therapeutic products and their pricing, as well as hepatitis C treatment and pricing trends globally.

### About the author

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## Larger, Deeper, and in Real Time: Applications of Machine Learning and Natural Language Processing on Electronic Health Records to Learn From the Patient Journey at Scale

### Signal IN BRIEF

- Applications to understand outcomes for patients with rare biomarkers, to identify at-risk populations, and to address inequities in care delivery and research all require large-scale and detailed real-world data to provide precise estimates in all relevant subgroups to assist decision making.
- Conventional data sources such as claims data may provide information at scale but lack the clinical depth that unstructured electronic health records data (eg, clinical notes, pathology reports) offer, such as information about biomarker results.
- Real-world data are not always patient experience data and improved mapping of the patient experience journey—from the first interaction with the healthcare system to treatment and side effects—has implications for the design of real-world data studies.
- Researchers have been able to produce case studies in which machine learning and natural language processing are applied to electronic health records to obtain real-world data and real-world evidence quickly and at scale, increasing stratification cohort sizes (scale), keeping up with standard of care (speed), and improving representation of underserved populations (depth).
- Achieving this will take human and artificial intelligence collaboration, which could be in the form of clinicians integrating artificial intelligence into their clinical practice or engaging patients and determining the purpose, implementation, and interpretation of these models.

ISPOR's 2023 annual conference in Boston, MA in May had the use of artificial intelligence (AI) in health economics and outcomes research (HEOR) as a running theme. The *Signal* session presented there, "[Larger, Deeper, and in Real Time: Applications of Machine Learning and Natural Language Processing on Electronic Health Records to Learn From the Patient Journey at Scale](#)," was no exception. Featuring 3 case studies, the session sought to describe the pragmatic impact of applying machine learning and natural language processing on electronic health records (EHRs) to generate and accelerate insights on the patient journey.

According to panel moderator Joe Vandigo, MBD, PhD, Applied Patient Experience, "if engaging patients tells us about their experiences, machine learning and natural language processing can help us understand how representative that experience is at scale, not only in a way that's rapid so that we can incorporate it into decision making, but also in a way that we can bring in populations that we're currently not able to reach."

As Vandigo explains, the patient journey is often thought about through the lens of patient experience data—that is, aspects of the patient experiences that matter to the patient. These can include symptoms, the natural history of the disease, patient experience with treatments, and patients' quality of life and individual functioning. Real-world data (RWD) "can absolutely describe what patients experience with a disease or condition. But often those things aren't what matters to the patient." However, there is overlap in these aspects and the collection and analysis of RWD should be informed by patient priorities. Machine learning and natural language processing "are absolutely useful" in identifying patterns around when individuals first interact with the healthcare system and describe common treatment pathways and side effects.

Vandigo states that to achieve the best ways to gather RWD will take human and AI collaboration, which could take the form of clinicians integrating AI into their clinical practice or the form of engaging patients. At the same time, researchers must be able to explain the purpose, implementation, and interpretation of these models—how clinicians integrate AI into their practice and where researchers should be engaging patients and other stakeholders in machine learning and natural language processes. Vandigo argues that for the latter, "there is a need for engaging them continuously."

Audience polling conducted during the session found many of those who attended would prefer that the AI they use would be assistive (helping patients make decisions and acting as a second set of eyes for clinicians and researchers) rather than autonomous (AI making clinical treatment decisions that impact patient care and outcomes).

### Getting AI Into Clinical Workflows

Ravi Parikh, MD, MPP, an oncologist at the University of Pennsylvania, runs a lab called the Human Algorithm Collaboration Lab that focuses on the “last mile” problem of AI, trying to bring AI into clinical care workflows. Rather than building “the latest and greatest” deep-learning algorithm, Parikh says he and his colleagues are testing simpler algorithms, bringing them to the point of care faster to show their use case.

The work done by this group has convinced Parikh that AI not only needs humans but actually benefits from human interface to help generate it, especially at the point of care. He described how the EHR he encountered as an oncology resident had a low-level machine learning algorithm that generated a readmission risk score for each patient based on diagnosis codes. While some clinicians might find that risk assessment useful, he says he found it distracting because patients with cancer were always scored as having a high readmission risk. “If I listened to it, I would have never discharged anyone from the hospital.”

Furthermore, the EHR’s risk assessment “didn’t correspond to levels of risks that actually matter to me,” Parikh says, and “probably wasn’t designed with an end user in mind because it doesn’t really tell the clinician what to do.” Not being tied to a clinical intervention “is one of the big bugaboos of why AI algorithms largely are viewed as extra, more sophisticated bells and whistles, as opposed to something that actually helps clinicians in their workflow.”

While clinicians are seeking to use AI in an assistive way, Parikh points out that because humans are the end users, the results are still subject to human biases. “We ought to be structuring the AI in ways that can help counter some of those heuristic and cognitive biases that are responsible for suboptimal clinical decision making, rather than just generating the most accurate tool,” he says.

When designing a human machine collaborative system, Parikh and his colleagues have found there are 3 important stakeholders: (1) the machine itself; (2) the data scientists; and (3) the clinicians.

And when considering the clinicians, although they do see all the patients’ information and theoretically have access to years of training, “there’s a lot of inter-clinician bias in terms of decision making and variability.” To engage team members on the human side needs communication between clinicians, behavioral scientists, and mixed-methods researchers to figure out how to design workflows and use technologies like AI in clinical decision making.

As Parikh points out, “even if you had the perfect machine and the perfect 100% human accuracy all the time, if you deploy it in a context that’s not ready for use (eg, if you don’t have an intervention to tie to the prediction or the diagnosis, or if it’s operationalized as a column in your EHR, or as a bell and whistle in addition to all the other bells and whistles in the intensive care unit), then it’s unlikely to engender impact.”

### KEY TAKE-AWAYS

- Machine learning and natural language processing can help researchers understand how representative a patient’s experience is at scale, in ways that are rapid enough so learnings can be incorporated into clinical decision making and allow for bringing in populations that researchers are currently not able to reach.
- Artificial intelligence should be assistive rather than autonomous. Artificial intelligence not only needs humans but actually benefits from human interface to help generate it, especially at the point of care.
- Advances in machine learning and natural language processing enable researchers to extract information from patient charts with greater scale, flexibility, and efficiency.
- Natural language processing and machine learning can unlock the power of electronic health records but it is not a straightforward procedure and researchers should not put all their data into a black box and blindly accept the results.
- While clinicians are seeking to use artificial intelligence in an assistive way, because humans are the end users, the results are still subject to human biases. Artificial intelligence needs to be structured in ways that can help counter some of those heuristic and cognitive biases responsible for suboptimal clinical decision making.

### Seeing the Text From EHRs as Data

Selen Bozkurt, PhD, a biomedical informatics researcher formerly at Stanford University and now at Emory University, says while EHR data are rich, they are mostly in a text format, adding that “even radiology images have text reports.”

To automatically learn from this text data will take natural language models. “As text is our input, it can be a rule-based model using terminologies; it can be a machine learning model using distributional semantics; or it can be a large language model using transformers like ChatGPT,” Bozkurt says. All of these models convert text into numerical format to use for other computational purposes, such as classification or prediction, or generating other texts.



“To achieve the best ways to gather real-world data will take human and AI collaboration, which could take the form of clinicians integrating AI into their clinical practice or the form of engaging patients.”

— Joe Vandigo, MBD, PhD

One of Bozkurt's first research studies, about 10 years ago, was in converting the text in mammography reports into structured data fields. More recently, she and her colleagues investigated extracting missing cancer stage information from cancer registries, as they had found 30% of the EHR records were missing this information. They wound up reprocessing the notes using a knowledge base, purging redundant text and dividing the nodes of the base into smaller pieces such as words, sentences, or phrases. “This knowledge base part is important, because we want to have full control of what we are doing,” Bozkurt says. “We didn't want something to make things up or hallucinate.” The base was created using expert knowledge ontologies, which Bozkurt states are a “great source of knowledge plus some distributional semantics.”

In the end, Bozkurt and her colleagues were able to extract 70% of missing pathological stage information and 30% of missing clinical stage information. “It was not perfect but it was pretty promising as a proof of concept,” she says.

Bozkurt says natural language processing and machine learning can unlock the power of EHRs “but it is not a straightforward procedure,” and involves “making several careful decisions. It is not like all the data get put into a black box and we accept everything blindly that they produce.”

### Getting That Data Faster

Katherine Tan, PhD, a senior data scientist at Flatiron Health, says the remaining challenge of using EHR data is the huge amount of unstructured data they contain. While a trained abstractor could perform chart reviews to manually identify and extract the technical terms, this process is resource-intensive and costly. As a result, tradeoffs are made, mainly sacrificing speed.

“For example, consider a rare population where to identify just a single patient of interest requires surfacing an enormous volume of text,” Tan says. “To be able to find enough patients to power analyses, there is this constant expense of keeping up with the latest standard of care and how quickly we're able to add new variables to our data set.”

Advances in machine learning and natural language processing enable researchers to extract information from patient charts

with greater scale, flexibility, and efficiency. These natural language extraction models use natural language processing to sift through the enormous volume of text and extract the most relevant snippets. The snippets are then fed into a machine learning algorithm that outputs the clinical outcome of interest such as a biomarker name or an environment mutation detail. “The application here is not predicting information, not inferring information based on the patient chart or generating text,” Tan says. “It is a scalable and automated way of extracting information from the patient chart similar to how an abstractor would. At the end of the day, machine learning is a tool to help us do our jobs better. And for real-world evidence, that could mean getting higher quality data faster.”

ISPOR members continue to explore the uses, challenges, and parameters of AI in producing real-world evidence, sharing results through [Value in Health](#) and conference presentations on topics such as [AI in drug launches](#), [HTA assessments](#), and [HTA assessments and drug pricing](#).

ISPOR started the [Signal program](#) to bring a broader understanding of innovation (beyond product innovation), with the goal of putting these issues front and center for the HEOR community. Each episode in the series is a self-contained installment and not dependent on the previous episodes. However, all of them are connected by an intent to look at the concept of innovation and experience with it from different groups of healthcare stakeholders, building foresight into how these innovations might impact healthcare decision making in the next decade.

The ISPOR [Signal Program](#) is now delivered live at our annual in-person conferences. The next ISPOR [Signal](#) titled, “EU Joint Clinical Assessment: One for All and All for One?” is scheduled to take place at ISPOR Europe 2023 on November 13, 2023 at 10:15-11:15 in Copenhagen, Denmark.

### Read more about past [Signal](#) events in [Value & Outcomes Spotlight](#)

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### For more information and to register

[www.ispor.org/signal](http://www.ispor.org/signal)

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## HEOR NEWS

**1 Billions Left Behind on the Path to Universal Health Coverage** (WHO)

The World Health Organization (WHO) and the World Bank, in their 2023 Universal Health Coverage Global Monitoring Report, have found that over the past 2 decades less than a third of countries have improved health service coverage and reduced catastrophic out-of-pocket health spending.

[Read more](#)

**2 Patient Safety and Surgical Innovation: Why New Isn't Always Better** (NICE)

Jane Blazeby, professor of surgery, University of Bristol, and the NIHR Bristol Biomedical Research Centre, says surgeon innovators in her research uniformly shared "optimism bias" of the theoretical benefits of an innovation, and in surgical consultations, only a minority of surgeons communicated the uncertainty about safety or told the patient that they had limited experience with a new procedure.

[Read more](#)

**3 First WHO Report Details Devastating Impact of Hypertension and Ways to Stop It** (WHO)

In its first-ever report on the global impact of high blood pressure, the World Health Organization found that 4 out of every 5 people with hypertension are not adequately treated. But if countries prioritize prevention, early detection, and effective management of hypertension at the primary care level, the economic benefits of improved hypertension treatment programs outweigh the costs by about 18 to 1.

[Read more](#)

**4 Neighborhood Context and Children's Healthcare Utilization and Health Outcomes: A Comprehensive Descriptive Analysis of National Survey Data**

(Health Affairs Scholar)

Using the nationally representative sample of children from pooled 2013–2017 Medical Expenditure Panel Survey data linked to the census-tract-level Child Opportunity Index 2.0 (a composite measure of neighborhood health, education, and socioeconomic conditions), researchers found that children living in lower-opportunity neighborhoods had the highest rates of poor physical and mental health status and fewest ambulatory care visits but accounted for the highest share of emergency department visits.

[Read more](#)

**5 Unaddressed Functional Difficulty and Care Support Among White, Black, and Hispanic Older Adults in the Last Decade** (Health Affairs Scholar)

In looking at community-dwelling older adults who had difficulty with, but lacked assistance for, self-care, mobility, and

household activities before and after the Affordable Care Act, researchers found the prevalence of Black and Hispanic people with functional difficulties lacking corresponding care support was consistently 1.5 times higher than that of White people.

[Read more](#)

**6 What Is the Impact of the COVID-19 Pandemic on Tuberculosis?** (Lancet Global Health)

In trying to estimate whether the death rate from tuberculosis will rise, researchers doing a longitudinal analysis in Indonesia found that while the tuberculosis case notification rate decreased by 26% and tuberculosis treatment coverage dropped by 11% during the pandemic, the all-cause death rate during tuberculosis treatment did not change significantly. However, these researchers theorize that undiagnosed individuals with tuberculosis may have been dying from COVID-19.

[Read more](#)

**7 Africa CDC and France Sign Memorandum of Understanding to Strengthen Public Health Systems in Africa** (Africa CDC)

The goals of the memorandum of understanding are to strengthen Africa's Centres for Disease Control and Prevention capacity; support the development of national public health institutes; enhance disease surveillance and emergency response capacities; promote the local manufacturing of vaccines, diagnostics, and therapeutics; support workforce training; and foster research partnerships between French and African institutions.

[Read more](#)

**8 Women Less Likely to Be Given CPR Than Men in Public Places** (European Society for Emergency Medicine (EUSEM))

Bystanders are less likely to give cardiopulmonary resuscitation (CPR) to women than men, particularly if the emergency takes place in a public area. Researchers found only around half of patients received CPR from a bystander (54%), with women being slightly less likely to be given CPR (52% of women compared to 55% of men).

[Read more](#)

**9 Global and Regional Estimates of Genital Human Papillomavirus Prevalence Among Men: A Systematic Review and Meta-Analysis** (Lancet Global Health)

Almost 1 in 3 men worldwide are infected with at least one genital HPV type and around 1 in 5 men are infected with one or more HR-HPV types, with HPV prevalence high in young adults, reaching a maximum between the ages of 25 years and 29 years.

[Read more](#)



## ISPOR Conferences and Events

# ISPOR Europe 2023 | 12-15 November

Bella Center Copenhagen, Copenhagen, Denmark



ISPOR Europe 2023 is shaping up as THE not-to-be-missed European conference of the year with a host of thought-provoking sessions and opportunities to immerse yourself in the health economics and outcomes research (HEOR) space. Network with HEOR expert stakeholders, global thought leaders, and your peers to explore how we share value that is sustainable for health systems, patients, and technology developers.

Session highlights include high-profile plenary sessions tied to the conference theme “*HEOR at the Nexus of Policy and Science*” led by program committee co-chairs, offering insightful commentary on the pressing issues in healthcare today.

### Join us for these Plenary sessions:

**Monday, 13 November | 8:30 CET**

#### European Health Data Space: RWE Put to Work for Public Health

Moderator: **Steffen Thirstrup, MD, PhD, CMO**, European Medicines Agency

**Tuesday, 14 November | 8:30 CET**

#### The New Pharma Legislation Proposal: The Good, the Bad, or the... ?

Moderator: **Anja Schiel, PhD**, Norwegian Medicines Agency

**Wednesday, 15 November | 11:30 CET**

#### The Calm Before the Storm? Delivering the New Reality for EU HTA

Moderator: **Adrian Griffin, MSc**, Johnson & Johnson

### Spotlight sessions will highlight areas of innovation in HEOR:

- Navigating Challenges and Seizing Opportunities: Leveraging Multiple RWD Sources in External Control Arms for HTA and Regulatory Decision Making
- What Should Value Assessment of New Antibiotics Look Like in the Context of Pull Incentives? The How, What, and Where Next for Antimicrobial Resistance and Health Technology Assessment
- Behavioral Economics to Inform Healthcare Decisions

### View a snapshot of our in-person short courses:

- The Role of Digital Endpoints in the Value Generation for Health Technologies
- Valuation of Innovative Drugs
- Unveiling the EU-HTA Regulation: A Deep Dive Into the Joint Clinical Assessment

View all in-person short courses [here](#).



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 More at [www.ispor.org/ISPOREurope2023](http://www.ispor.org/ISPOREurope2023)

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## ISPOR Conferences and Events

# ISPOR 2024 | May 5-8

Georgia World Congress Center, Atlanta, Georgia, USA



### The Leading Global Conference for Health Economics and Outcomes Research

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Session Abstract Submission Closes: December 14, 2023

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ISPOR short courses are designed to enhance knowledge and techniques in core health economics and outcomes research (HEOR) topics as well as emerging trends in the field. Short courses offer 4 or 8 hours of premium scientific education and a digital course book. Active attendee participation combined with our expert faculty creates an immersive and impactful virtual learning experience. Short courses are not recorded and are only available during the live broadcast.

#### Upcoming ISPOR short courses include:

**October 17-18 | 10:00AM – 12:00PM EDT (Virtual)**

#### Understanding Survival Modeling With Application to HTA

*What you will learn in this intermediate level course:*

- Understand the relationships between key time-to-event functions and their use in economic modeling.
- Examine various approaches to alternative parametric survival models employed in cost-effectiveness analyses.
- Consider the differences when selecting survival models for cost-effectiveness analyses and the differences between partitioned survival and Markov-based cost-effectiveness models.

**October 25-26 | 10:00AM – 12:00PM EDT (Virtual)**

#### Patient-Focused Medical-Product Development: It's Here. Are you Ready for it?

*What you will learn in this introductory level course:*

- Get a foundational introduction to patient engagement (PE) in medical-product research and development by defining the terms, providing historical context, and illustrating its significance throughout ISPOR's HEOR taxonomy.
- Acquire tools to plan and implement meaningful PE activities in their respective areas of research (eg, clinical development, epidemiology, health economics, real-world evidence, etc).
- Build skills needed for those responsible for doing the engaging versus those using PE in research.

**November 1 | 10:00AM – 2:00PM EDT (Virtual)**

#### Use of Propensity Scores in Observational Studies of Treatment Effects

*What you will learn in this intermediate level course:*

- Recognize the ways propensity scores can be used to mitigate confounding through standard observational approaches (restriction, stratification, matching, regression, or weighting).

- Understand the advantages and disadvantages of standard adjustment relative to propensity score-based methods.
- Learn the details of propensity score methodology (variable selection, use, and diagnostics) and risk adjustment models that collapse predictors of outcomes and their use relative to propensity scores.

**December 6-7 | 10:00AM – 12:00PM EST (Virtual)**

#### Transportability Methods for Clinical Trials and External/Indirect Comparisons

*What you will learn in this intermediate level course:*

- Understand and evaluate the plausibility of the assumptions required for transportability analyses for extending inferences from a clinical trial to a target population and for conducting external comparisons.
- Appreciate the advantages and disadvantages of different transportability methods (eg, weighting, outcome modeling, and doubly robust methods).
- Be able to implement the methods in data and interpret their output.

**December 12-13 | 10:00AM – 12:00PM EST (Virtual)**

#### Structured Expert Elicitation for Healthcare Decision Making

*What you will learn in this introductory level course:*

- Understand the fundamentals of structured expert elicitation (SEE): what it is, when to use it, and the resources required.
- Understand key drivers of methodological decisions when planning an SEE exercise.
- Utilize the publicly available SEE tool developed by the University of York and Lumanity.

 [View all short courses](#)

# ISPOR Education

## ISPOR Webinars



**October 10 | 10:00AM – 11:00AM EDT**

### External Control Arms: Application, Key Methods, and Acceptability

*What you will learn in this webinar:*

- Understand when and why external control arms (ECA) are used and what are acceptable types of data and methods to build ECAs.
- Understand terminology such as Target Trial Emulation, ECA, historic control arms, simulated and synthetic control arms, and be aware of the key considerations when performing ECA, including methods, assumptions and limitations of ECAs.
- Understand the circumstances under which ECAs are accepted from regulatory and HTA bodies.

**October 11 | 10:00AM – 11:00AM EDT**

### How Does Biosimilar Availability Create Value for the Patient? A Conversation About Avenues to Widen Access to Biologics

*What you will learn in this webinar:*

- Gain knowledge from real-life examples on how biosimilar adoption has positively impacted care.
- Integrate testimonials from patient, policy, and healthcare professional representatives on the topic of biosimilar value.
- Reflect on what is further needed to increase the value proposition from biosimilar entry for patients.

**October 13 | 12:00PM – 1:00PM EDT**

### Payer Views on Prescription Digital Therapeutics in the United States and Canada

*What you will learn in this webinar:*

- Understand how different US payers evaluate prescription digital therapeutics (PDTs).
- Understand different stakeholder perspectives regarding PDT appraisals and emerging PDT priorities.
- Consider challenges for integration of PDTs into health systems.

**December 5 | 11:00AM – 12:00PM EST**

### Tokenization in Clinical Trials: Benefits and End-to-End Enablement

*What you will learn in this webinar:*

- Understand tokenization, its benefits and applicability, including how tokenization can be used to follow clinical trial participants in the real world.
- Gain an understanding of the key considerations and steps needed to tokenize clinical trials, including necessary interactions with clinical trial sites.
- Learn how to create linked datasets and how to leverage it for generating fit-for-purpose RWE with appropriate study designs.

**December 7 | 9:00AM – 10:00AM EST**

### Data Privacy and Digital Health Implementation: The Patient Perspective

*What you will learn in this webinar:*

- Understand patient involvement in new digital health initiatives.
- Learn about data sharing as it relates to privacy and security from the patient perspective.
- Recognize expectations from patients to get individual digital health feedback information.

**December 8 | 10:00AM – 11:00AM EST**

### Digital Technologies for Health Systems: The African Experience

*What you will learn in this webinar:*

- Understand how to outline the rolling out digital health technologies experience within the African continent.
- Discuss the role of big data analytics in economic evaluations of health interventions in African countries.
- Describe the future prospects of digital health technologies in the African context.

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# PREPARING YOUNG HEOR PROFESSIONALS

## TO BUILD A BETTER FUTURE

By John Watkins, PharmD, MPH, BCPS,  
Managed Care Perspectives, LLC, Bothell, WA, USA



Today's healthcare environment is changing rapidly. Health economics and outcomes research (HEOR) educators and mentors must prepare their students and young professionals to manage change as they assume future leadership roles. Academic programs will revise curricula to incorporate new research methods and modes of learning. Mentors should be prepared to help graduates negotiate career patterns very different from the ones they have followed. Reducing health disparities will require a diverse HEOR workforce able to analyze patient heterogeneity across new dimensions of value. As the workforce diversifies, ISPOR is revising and updating its framework of basic competencies for HEOR professionals.

## What will change?

Change in the science is occurring at several levels. Growth in the underlying knowledge of biology is followed by developments in pharmaceuticals and medical technology. Pharmaceutical companies address new targets with novel drugs. New technologies like gene and cell therapies appear. Improving health information systems will increase interoperability and real-time data exchange between health systems and payers. Digital health technologies and artificial intelligence (AI) promise to transform the way health professionals work. Robotics and bioengineering will support advances in remote surgery, prosthetics, and more.

Measuring outcomes and modeling cost-effectiveness of these new practices will require creative approaches that incorporate societal impact and new ways of measuring value to patients and caregivers. Technology will drive innovative clinical trial designs and outcome measures. Facilitated by cloud-based analytics, large database studies will proliferate, along with opportunities for interregional collaboration and comparison of methods and results. Since new health technologies usually increase cost, the global problem of affordability will have to be addressed.

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**“HTA institutions are slowly gaining traction and requiring clinical and economic evidence beyond regulatory evidence, increasingly incorporating real-world evidence into decision making.”**

– Federico Augustovski, MD, MSc, PhD

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COVID accelerated adoption of remote work technologies. Social and economic change has created a “new normal” in workplace design and expectations. In the [March/April issue of Value & Outcomes Spotlight](#), talent recruiting specialist Poppy King predicted a hybrid work environment with staff in office 60% to 80% of the time. Virtual work expansion lets employers hire talent from around the world, increasing workplace diversity. HEOR professionals that build models for settings where they have never lived will need a level of cultural competence not previously expected of them.

Young professionals will learn to work with machines in new ways, using AI assistance for routine tasks. Augmented reality will provide a richer experience when meeting with distant colleagues, more like being in the same room. Gen Z is bringing new expectations to the workplace. Because they have interacted with screens since infancy, they read, process information, and relate socially in different ways. They have a new emphasis on work-life balance. HEOR professionals will need to adapt and be comfortable in a variety of settings. Workforce diversity will increase as more students from minorities, low- and middle-income countries, and more women enter the field.

“Latin America tries to adapt to the current and upcoming challenges that high-income countries initially face,” notes Federico Augustovski, MD, MSc, PhD, Director, Department of Health Technology Assessment and Health Economics at the Instituto de Efectividad Clínica y Sanitaria (IECS), University of Buenos Aires, and the first ISPOR President from Latin America. “HTA institutions are slowly gaining traction and requiring clinical and economic evidence beyond regulatory evidence, increasingly incorporating real-world evidence into decision making.” Like their global counterparts, Latin American HEOR professionals have changing attitudes toward work. “Newer generations have a different value mindset, with weaker attachments to work and stronger ties to hedonism,” Augustovski observes. “Specific areas of knowledge growth include those related to precision or personalized medicine, data science, coupled very tightly to real-world evidence.”

“I envision three major changes graduates will face in the next 10 years,” Anirban Basu, PhD, MS, Director of the University of Washington’s CHOICE Institute, predicts. “Greater integration of AI-related technologies in HEOR work and evidence generation, the changing landscape of financing medical technologies, especially in the United States, and adapting to nontraditional work environments. Hybrid work means less commute, but it may cause more professional isolation.” Basu adds that, “Each cohort is different. We spend a lot of time during the first year getting to know them well. Overall, the past decade has certainly seen a shift in how new students learn and we try to adapt to new modes of instruction to keep up with such changes.”

## Formal Academic Programs

Doctoral and master’s degree programs will continue to be the place to learn core HEOR skills. Hybrid fellowships are offered by pharmaceutical manufacturers in partnership with academic HEOR programs. Fellows usually spend a year at university earning a master’s degree, then a year with the sponsor’s HEOR staff. Postdoctoral research fellowships are offered in academic and other research settings.

HEOR doctoral programs focus on research methods and underlying concepts. For example, the required courses for a PhD in HEOR at the CHOICE Institute include applied biostatistics, survival data analysis, epidemiologic methods, large database research methods, causal inference from observational data, pharmacoepidemiology, economic and outcomes evaluation in health and medicine, health economics, and pharmaceutical policy analysis. The University of York offerings for a PhD in health economics include microeconomics, econometrics, mathematical research methods, and health economics for research.

Shorter programs for working professionals include remote learning certificate programs and short programs offered online or alongside major professional society meetings. ISPOR offers a number of short courses at its major meetings and online short courses (paid) and webinars (free to ISPOR members in the [HEOR Learning Lab](#)). These webinars allow those working in related fields to explore the HEOR profession with minimal time commitment and expense.

Academic programs will need to expand core offerings to address coming changes and influence health policy. Mike Drummond, MCom, DPhil, professor emeritus at the University of York's Centre of Health Economics in the United Kingdom reflects on methodology. "The main challenges are likely to be driven by changes in payers' evidence needs and the characteristics of products being assessed. Payers will ask for more information in the future, particularly on cost-effectiveness, but clinical evidence on new products seems to be getting less and less, owing to 'fast-track' approvals and smaller patient populations, such as gene therapies and personalized medicine. The greatest learning needs in the future are likely to be interpreting nonrandomized real-world data, validation of surrogate endpoints, understanding the types of uncertainty and how they can be addressed, and various types of outcomes-based managed entry schemes, which require actuarial skills."

Scott Ramsey, MD, PhD, director of the Hutchinson Institute for Cancer Outcomes Research, predicts the need for targeted training for increasingly specialized research. "As real-world data expand and move closer to real-time data capture, HEOR professionals will have to be much more facile with databases. This includes merging databases, being better at extracting data to more closely represent real-world patient populations that match the US Food and Drug Administration's labels. Real-world data will be used to actively monitor use and outcomes of costly new therapies. Gene therapy will be at the forefront of this trend. I think formal education will need to move away from broad-based master's and PhD programs to specialized training in data science, modeling, and clinical epidemiology. Training will need to be shorter and more focused to attract students. Demand for multiyear degrees that cost students hundreds of thousands of dollars is already waning."

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**"The past decade has certainly seen a shift in how new students learn and we try to adapt to new modes of instruction to keep up with such changes."**

— Anirban Basu, PhD, MS

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Drummond, in his role as Editor-in-Chief of *Value in Health*, cautions against relying too much on journals for guidance. "Most journals reflect the changing environment rather than guide it, since they consider whatever papers are submitted. To drive change, some journals (eg, *Health Affairs*) have established blogs, which enable them to publish highly relevant material very quickly. *Value in Health* has themed sections on topics that the journal feels are important or emerging. Some of these reflect the ISPOR's Top 10 HEOR Trends report."

"Our students come out with great tools in the field. I want to strengthen their toolkit and policy evaluation," says Sean Sullivan, PhD, BSc Pharm, professor and dean emeritus of pharmacy at the University of Washington. They need to be

"creative and extend the basic methodology" to address the coming changes.

"I see 2 big things happening in the United States in the next 10 years," Sullivan continues. "I see a lot of work on alternatives to the cost per QALY (quality-adjusted life year) framework, and we are going to learn how to apply those new methods and make them work. Then I see the Centers for Medicare & Medicaid Services (CMS) developing a value framework that all of us in the field will help develop, implement, and increment. The new final guidance from CMS opened the door for cost-effectiveness, so long as we don't use the QALY. We can do cost per 'life year gained.' We can do cost per 'health years in total,' the metric that [Basu, et al proposed](#)<sup>1</sup> or cost per 'equal value life year.' And there's even the possibility of advances in the [GRACE framework](#)<sup>2</sup> that will allow cost-effectiveness analysis that doesn't have an inherent bias to individuals who are disabled. And you could potentially crank into that a factor that would counteract the bias that the QALY has. The 2 areas of key focus for a graduate student are going to be ability to be creative and extend methodology, and policy. They need to be prepared to interact effectively with government."

### HEOR Education in Emerging Markets

Drummond notes additional considerations for emerging markets. "The main differences are the paucity of data for adapting or populating models to meet local needs, the lower sophistication of decision makers, and the lack of definition of decision criteria. Many of the [healthcare systems in low- and middle-income countries](#) are 'pluralistic,' having several healthcare systems operating alongside one another.<sup>3</sup> In very low-income countries, issues like equity and maintaining family income also have a greater emphasis, although equity is now becoming a big issue in high-income countries also." Scholarships for these students will remain a priority. Ramsey agrees that "we should be much more active in bringing underrepresented populations into research. Waiting until someone gets to graduate school misses the opportunity to have a much larger pool from earlier years of training."

Universities in Latin America are adapting curricula to the changing environment and needs. "On one side, both formal and practical training have to keep adapting to current platform demands," says Augustovski. "One of the good things of the *pandemia* was the push for improving online education in its platforms, educational tools, and contents. For example, our master's degree changed from mostly face to face teaching to an online-only program.<sup>4</sup> Curricula have to be flexible and adaptive, incorporating increasingly needed tools and skills such as real-world evidence design and analysis, or managed entry schemes. ISPOR can take advantage of its existing portfolio of products. For example, social media and new platforms can attract new audiences, or leveraging different channels like ISPOR's prestigious academic journals, namely *Value in Health* and *Value in Health Regional Issues*," he suggests.

### Experiential Training

Health professionals (MD, PharmD, etc) can enter the HEOR work force through manufacturer-sponsored fellowships. Shirley Quach, PharmD, completed the 2-year Managed Care Medical Communications/Managed Care Liaison fellowship at



Genentech and is now a payer-facing Value Evidence Lead at Novartis. “The fellowship engaged me in challenging, varied, and fun projects that pushed me to my fullest potential where I learned invaluable skills such as leadership, time management, collaboration across cross-functional partners, interpersonal skills, and written and verbal communications. It helped me achieve my career goals. The professional network that I built during my time as a fellow has provided me with access to job opportunities, career advice, new ideas, and valuable information.” she says.

Quach found the relationship and networking opportunities particularly valuable. Her program allowed flexible learning: “A fellowship gives you the opportunity to train in an extensive program, but also provides the flexibility of exploring opportunities in other functions to grow in your professional development journey. Fellowship is a time of absorbing knowledge and learning what your interests are. Your preceptors and mentors are there to support you in those goals and ambitions. As a fellow, it was much easier for me to work on projects and partner with other functions if I had an interest in learning more than in a regular job position. New graduates bring new perspectives and ideas. This is an opportunity to encourage them to be innovative and take risks. There may be uncertainty involved, but these choices can bring unexpected growth and success for the team and company.”

### Mentoring Future Leaders

Regardless of their formal education, young HEOR professionals need coaching and support now more than ever as they navigate today's turbulent world. Young professionals may be frustrated by the unpredictability of career paths. Tania Luna and Jordan Cohen suggest that “we are suffering from the career myth—a delusional belief in the outdated idea of linear career progression.”<sup>5</sup> They advise flexibility and a willingness to experiment and acquire transferrable skills. Mentors, particularly those that are older, should consider these changes when giving advice.

A mentor can be a veteran, mid-career, or young professional. Great mentors are passionate about their own work. “You have to love it or you won't become expert and you won't motivate people,” advises Sullivan. “Demonstrate passion yourself. Be really engaged in your mentees' work. Strive for growth in your field. Continue to invest in your own knowledge acquisition, maintaining your level of proficiency and knowledge. Love what you're doing to the point where you want to keep making yourself better.”

“Some of the things I value most in my mentors are their honest and candid advice, their experience and perspective, and their willingness to help me achieve my career goals,” says Quach. “The best mentors are those that remember what it was like to be a young professional themselves. Folks who have that characteristic are likely to be more generous with their time and a bit more patient with someone who is trying to learn,” adds Drummond. “Modesty is a good characteristic. Modest people realize that they don't know everything. Working with a mentee could represent a learning opportunity for the mentor as well.” Chad Murphy, Chief Clinical Officer at

Premiera Blue Cross reminds us to, “Listen and hear from the young professional what their goal is so you can tailor learning. A mentor cares about the profession and is someone that really likes to see people grow and develop and shine.”

Great mentors use their networks to help mentees. “Continue to grow your own professional network,” advises Sullivan. “It's always important to grow your sphere of people who like to talk and share ideas, and that takes time. It's not just people connected to you on LinkedIn or social media, but it's who you talk with—chat about what's going on in the world, ask how their projects are coming along. It is a deep connection with these folks. Connect to people who can help you in your career—and that never stops.”

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“The main challenges are likely to be driven by changes in payers' evidence needs and the characteristics of products being assessed.”

– Mike Drummond, MCom, DPhil

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“A mentor is a coach to facilitate achieving the path the mentee has chosen but not to add barriers or redirect them. Provide encouragement. Help them overcome fear of the unknowns as they move forward. A mentor helps broaden the mentees' view of the chosen field beyond the academic setting,” says Ed Wong, PharmD. “Mentors can be a calming presence in their mentees' lives. Acknowledge the tension and help them learn to walk the tightrope. Help them find their own passions.” Mentors should model involvement in professional societies and demonstrate the importance of volunteering. Use your own success to promote your mentees. Society meetings are a great place to do this.

### Ensuring Equity in HEOR Work and Education

Improving diversity is one of ISPOR's core values. The Society's mission, to *improve decision making for health globally*, includes addressing minorities that were previously overlooked, both globally and within local geographies. Two important factors in making this a reality are increased representation of minorities in the HEOR workforce and their inclusion in all phases of research and product development.

Since health economics is based in science and mathematics, improving workforce diversity must begin at lower levels of education, where there are established efforts to recruit minorities for science, technology, engineering, and mathematics (STEM) fields. We must interest these young people in our work, convince them that HEOR is relevant to their life experiences and can make a difference to their families and communities, and eliminate the barriers that hinder their education and entry into the STEM workforce. Strategies include visiting classrooms, working with teachers and trusted authority figures within the community, and disseminating information about STEM careers.<sup>6</sup>

When these young people enter college, health economists must recruit them. HEOR is a relatively abstract profession. Its tangible results are usually found downstream, in improved health outcomes through better decisions. Recruiters must answer the question, “Why should I study this complex field, and what difference will it make to the people that matter to me?” We must persuade undergraduates that a HEOR career offers rewards that are worth the extra time and investment. Geographic and financial barriers are even greater overseas. With established ISPOR affiliates (ie, consortia, networks, and chapters) on 6 continents, these members can play a major role in their countries’ universities.

Once minority students enroll in a HEOR graduate program, they should be offered opportunities to do research that impacts problems they care about. Faculty can engage in a mutual learning process to discover study opportunities. When research is completed, demonstrate its impact. Students from lower-income countries tend to establish a presence at certain universities, making it easier for others from their homelands to go there. HEOR programs can actively encourage this, and [ISPOR’s New Professionals Network](#) and the [ISPOR Student Network](#) are good resources.

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“The professional network that I built during my time as a fellow has provided me with access to job opportunities, career advice, new ideas, and valuable information.”

– Shirley Quach, PharmD

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Improving equity in healthcare involves health system-level analysis. Recognizing this, the Joint Commission has created an optional healthcare equity certification, which provides “the structure to guide your organization’s journey to achieving healthcare equity.”<sup>7</sup> This emphasizes the ongoing nature of the work. “Our health equity efforts have been a journey and there’s no destination,” says Mark Sparta, MPA, BS, president of Hackensack Meridian University Medical Center, the first hospital to receive certification. In addition to increasing diverse representation among hospital staff and leadership, Hackensack Meridian’s approach includes analysis of patient care data stratified by race and other sociodemographic factors. The results help the hospital tailor care to groups and individuals and support the institution’s community engagement efforts.<sup>8</sup>

Including minority representatives in all phases of research is a recent trend. Ashley Valentine, MRes, Co-Founder & President of Sick Cells, explains that “including diverse experts in clinical trial design, research, and healthcare decision making as a whole is an important step to achieving equity. When you increase diversity (racial, ethnic, gender, sexuality), you are increasing problem-solving ability. We all have different vantage points in how we experience healthcare. If a vantage point is

excluded from the design process, it will be missed. That’s how blind spots and biases are baked into research.”

This includes chronic disease patient communities, many of which are represented at ISPOR Patient Roundtables, where patients can discuss their specific needs. For example, the [May 2023 Roundtable](#) featured a discussion of sickle cell disease, a devastating condition that disproportionately impacts Black and African American people. In addition to the usual social determinants of health issues, disease-specific bias results from history and culture. “It was reported that only 1 in 4 patients with sickle cell disease receive the standard of care within the United States.” Among other strategies, the group discussed an initiative to design and implement university curricula that lessen bias toward patients with sickle cell disease.

The Innovation and Value Initiative has called attention to the lack of diverse patient and caregiver representation in clinical research. The goal of its Health Equity Initiative is “to drive multistakeholder consensus in research and value.”<sup>10</sup> Standard protocols for clinical research tend to minimize patient heterogeneity. Minority group patients may be more difficult to recruit and more likely to drop out of studies. Transportation and time off from work are common barriers to participation. More heterogeneity among subjects means a larger sample size for the required statistical power. As a result, findings are often less applicable to minorities. Use of digital health technologies can help overcome barriers to access for trial subjects and later for the communities they represent.

For example, a patient with sickle cell disease would probably be excluded from a trial of a new cardiovascular disease drug as a comorbidity that could confound results. Although most patients with sickle cell disease have cardiovascular disease, the drug’s impact on them will remain unknown. A physician considering prescribing the drug for a patient with sickle cell disease couldn’t predict whether the patient will benefit or suffer an adverse effect due to drug-disease interaction with the underlying sickle cell disease. By eliminating patients from a minority group, researchers may never learn how the drug will affect them physically, what impact it may have on their daily routines, or what their culture values are.

Inclusion of broader patient representation in all phases of research, including study design and planning, should become standard practice. Without the patient voice, we will never know their research priorities or what constitutes value for them.

### The ISPOR Competency Framework

HEOR is a relatively young field that people enter from a variety of backgrounds, as can be seen from the attendees at any ISPOR conference. Recognizing this, the Society has assumed leadership in defining a set of core competencies that should be demonstrated by graduates of academic HEOR programs. The [original version published in 2002](#) included 12 learning outcomes.<sup>11</sup> According to Laura Pizzi, PharmD, MPH, ISPOR’s Chief Science Officer, “An update to the Framework is currently underway. A survey will be conducted in October to assess the importance of each of the updated competencies and

relevance of each to the respondent's job. The workgroup is also planning to look at whether these constructs differ by country and/or region. There will be forum on the update at the ISPOR Europe 2023 conference in Copenhagen."<sup>12</sup>

As ISPOR has grown into a truly global organization, standardization is important. Employers should be confident that graduates of PhD programs in HEOR will be able to demonstrate these skills. Drummond, who was president of ISPOR during those years, notes that, "Acquiring a basic set of skills can only be a good thing since, as they develop, professions like HEOR need to determine a set of standards for their activities which, in principle, could be a way of auditing performance. I hope that the ISPOR framework will embrace much of the knowledge contained in the ISPOR Good Practices reports which, in my view, represent ISPOR's best output."

As the HEOR profession continues to grow in size and importance, we should be intentional about educating and mentoring a highly competent and diverse cohort of young professionals that are ready to take on the challenges healthcare will face in the coming decades. ISPOR will continue to provide creative ways for them to share knowledge and learn from others' experiences.

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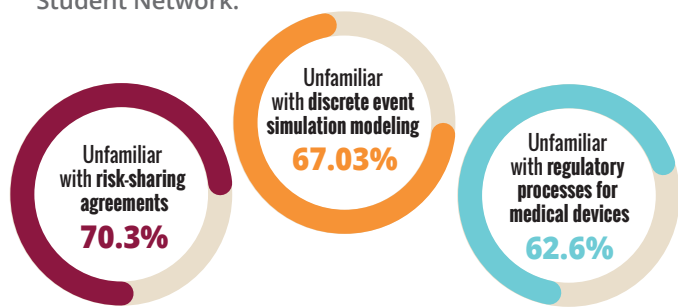
## By the Numbers: Developing Tomorrow's HEOR Leaders

Section Editor: The ISPOR Student Network

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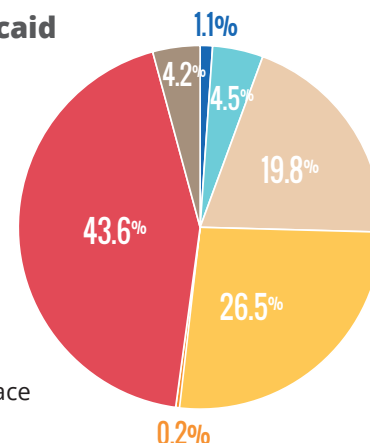
### Knowledge Gaps Among ISPOR Student Network Members

In a 2015 survey of 91 participants of the ISPOR Student Network:



### Equity in US Medicaid Beneficiaries for Fiscal Year 2019

- American Indian and Alaska Native
- Asian
- Black, non-Hispanic
- Hispanic
- Native Hawaiian and other Pacific Islander
- White, non-Hispanic
- Multiracial or other race or ethnicity



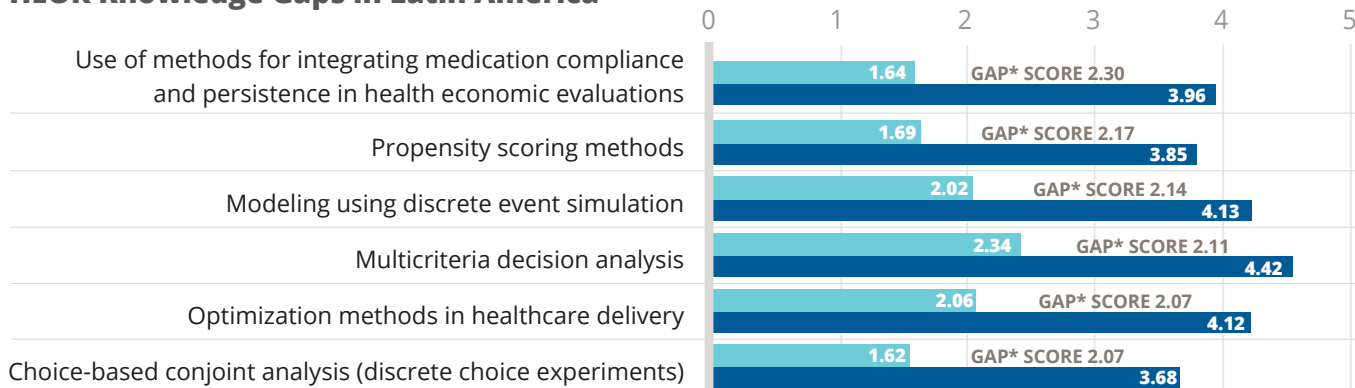
### Preferred HEOR Learning Formats in Latin America

#### Preferred formats/structures

1. Online learning programs/Continuing education	74%	6. Live webinars	45%
2. Online resources	67%	7. Mentorship/Preceptorship program	42%
3. Peer-reviewed literature reviews	52%	8. Expert speaker tour	29%
4. Workshops/Small-group learning sessions	52%	9. Newsletter	17%
5. Symposia/Conferences	46%	10. Other	4%

Note: n=89; 84% of total survey responses.

### HEOR Knowledge Gaps in Latin America



KEY: ■ Current Knowledge Score ■ Desired Knowledge Score

\* Gap (using individual response pairs)  
= Desired knowledge level - Current knowledge level.  
PRO indicates patient-reported outcome.

# Characterizing Telehealth Utilization From Administrative Claims in the United States Using a Standardized Definition

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Due to pandemic-related shifts in reimbursement and clinical practice, accurate standardized definition and integration of telehealth utilization is essential in health economic and outcomes research studies evaluating time periods from 2020 and beyond.

We created a telehealth definition in conjunction with a large national payer and report utilization metrics from a population with private insurance coverage.

## Telehealth and the COVID-19 pandemic

Before the COVID-19 pandemic response disrupted the healthcare system, the vast majority of patients in the United States had never used telehealth (TH) services.<sup>1,2</sup> The onset of the pandemic led to large decreases in patients' ability and willingness to participate in in-person care, driven by healthcare delivery policy changes as well as individual patient preferences. Both public and private payers expanded their coverage and reimbursement for TH services starting in March 2020 to encourage continuous access to the healthcare system. As a result, the United States experienced a large increase in TH use in both Medicare and commercially insured populations.<sup>3,5</sup> While TH supplied critical access to the healthcare system during the height of the pandemic, this increased accessibility did not compensate for the reduced utilization of healthcare overall, and had strong disparities along age, region, and other domains.<sup>6</sup> Research is needed to evaluate the effectiveness and safety of medical care delivered via TH and assess how it can best be implemented within the current healthcare delivery framework.<sup>7</sup>

While telehealth supplied critical access to the healthcare system during the height of the pandemic, this increased accessibility did not compensate for the reduced utilization of healthcare overall, and had strong disparities along age, region, and other domains.

Administrative claims are an important source of real-world data that can be used for TH-focused research. However, a wide variety of TH definitions and

identification algorithms are being used by different entities and cross-study comparisons are difficult.<sup>8-10</sup> In this article, we propose a standardized claims-based definition of TH in the outpatient setting and use it to investigate trends in TH utilization in a large US commercially insured and Medicare Advantage/Supplement population.

During the study period we identified approximately 75 million outpatient telehealth claims associated with approximately 12 million unique health plan members.

## Algorithm definition

We conducted a retrospective study using medical claims from the Healthcare Integrated Research Database (HIRD<sup>®</sup>) between January 1, 2006, and December 31, 2022. The HIRD contains longitudinal claims and eligibility data from a large national US health insurer offering health plans across many geographically diverse states and includes members with either commercial or Medicare Advantage/Supplement insurance representative of all 50 states. We used a limited dataset (information that excludes direct individual identifiers) in compliance with the Health Insurance Portability and Accountability Act Privacy Rule.

All analyses were descriptive. We evaluated the utilization of TH in an outpatient setting over time using a combination of place of service codes, Current Procedural Terminology (CPT) codes, CPT modifiers, Healthcare Common Procedure Coding System (HCPCS) codes, revenue codes, and certain tax identification numbers (TaxIDs) from known TH providers. The presence of at least one of the below codes was used to classify a claim as TH:

- Centers for Medicare & Medicaid Services (CMS) Place of Service<sup>11</sup> - '02' or '10'
- CPT and HCPCS codes - **'98966'\***, **'98967'\***, **'98968'\***, '98969', '98970', '98971', '98972', '99367', '99368', '99371', '99372', '99373', '99421', '99422', '99423', **'99441'\***, **'99442'\***, **'99443'\***, '99444', '99446', '99447', '99448', '99449', '99451', '99452', '99453', '99454', '99457', '99458', '0188T', 'G0406', 'G0407', 'G0408', 'G0425', 'G0426', 'G0427', 'G0459', 'G0508', 'G0509', 'G2010', 'G2012', 'G2061', 'G2062', 'Q3014', 'T1014', 'S0320', 'G0071', 'G0181', 'G0182', '0488T', '0074T', '0488T', '0206T', '93050', '96120', '96146', 'G2250', 'G2251', 'G2252', 'G0425', 'G0426', 'G0427'
- CPT and HCPCS modifiers - 'GT', 'GQ', 'GO', '95', '93'
- Revenue Codes - Starting with '078'
- TaxIDs - [Confidential]

A subset of codes (bolded & starred) was used to identify audio-only TH visits. CMS enacted a policy change effective March 2020 that introduced coverage for telephone evaluation and management services.<sup>12</sup>

**Algorithm application**

During the study period we identified approximately 75 million outpatient TH claims (fully adjudicated and paid) associated with approximately 12 million unique health plan members. Of the associated members, 88% were commercially insured, 6% had Medicare Advantage plans, and 4% had Medicare Supplement plans (other Medicare plans accounted for the rest). Approximately 97% of all TH claims since 2006 occurred in 2020 (33%), 2021 (33%), and 2022 (31%). In 2019 to 2022, the annual share of outpatient claims designated as TH was 0.1%/4.8%/4.1%/3.8%, respectively. Since the vast majority of TH claims occurred from 2020 onward, the analyses presented focus on that time period.

The majority of claims were identified as TH through use of either CPT modifiers or place of service codes (these are not mutually exclusive; a claim can be flagged as TH through one or more codes). The share of claims with a designated TH place of service code increased from less

than 50% to more than 70% since March 2020. An additional place of service code ("10") was authorized by CMS starting January 2022, and we have observed utilization of this code over the course of that year.<sup>13</sup> Except for a few months, TH claims identified via TaxIDs contributed a negligible amount of TH utilization (Figure 1).

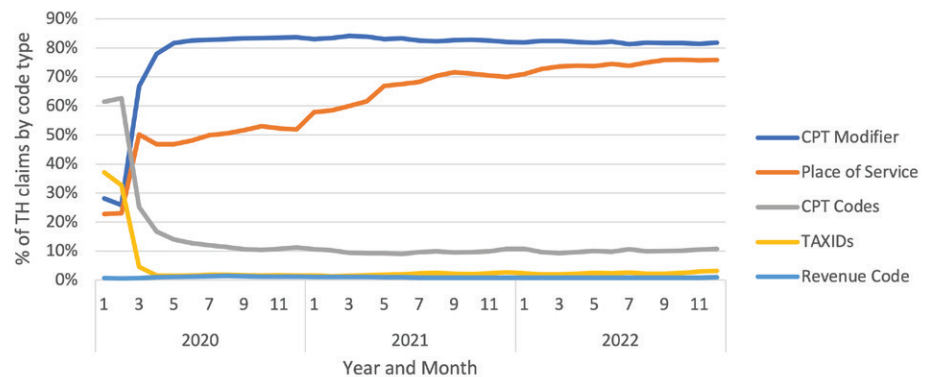
Outpatient services are classified using a modification of the Berenson-Eggers Type of Service (BETOS) categorization involving 10 mutually exclusive categories.<sup>14</sup> The distribution of TH claims across BETOS categories changed during the first few months of the pandemic (due to new coding practices having to evolve), with almost all falling under *Office Visits (Evaluation & Management)* and *Physician Other Services* (e.g., CPT codes associated with hospital

and home visits; specialist visits) since that point (Figure 2).

Insurance type affected TH utilization, which was higher among commercially insured compared to Medicare Advantage members (Figure 3). This analysis also indicates that TH utilization peaked at around 8% of all outpatient claims in the first half of 2020, exhibits a seasonal pattern, and remains at 2% to 4% through 2022 in this population. National reports (through August 2021) show similar trends in overall and age-stratified utilization.<sup>1</sup>

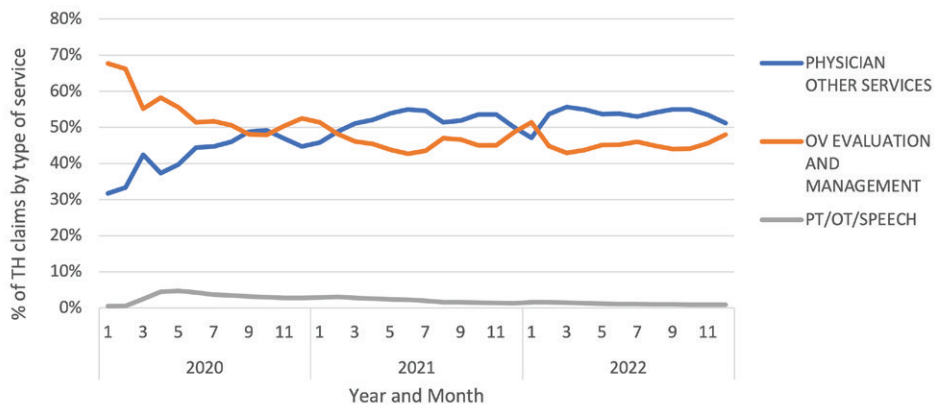
Approximately 2% of TH claims were for audio-only visits based on submitted codes. Distributions by insurance type in 2020 through 2022 are shown in Figure 4, indicating highest utilization in the Medicare Advantage population.

**Figure 1. Distribution of telehealth claims by code type**

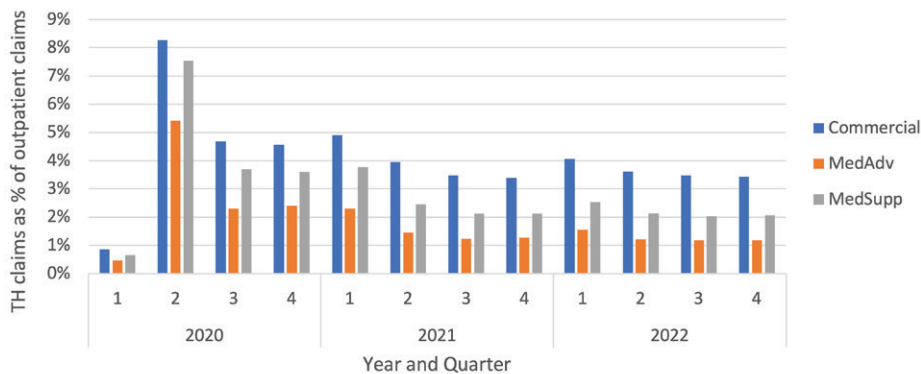


Notes: A claim can have more than one code type for telehealth identification; the categories listed in Figure 1 are not mutually exclusive and can sum to more than 100%. CPT indicates Current Procedural Terminology; TAXIDs, tax identification numbers; TH, telehealth.

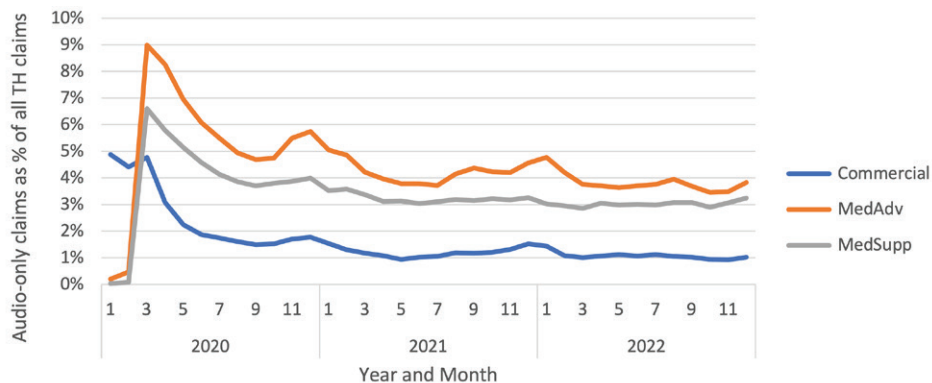
**Figure 2. Distribution of telehealth claims by type of service**



Note: The figure shows the top 3 types of service contributing to TH claims. The remaining types of service (eg. procedures, lab tests) accounted for the small remainder. OT indicates occupational therapy; OV, office visit; PT, physical therapy; TH, telehealth.

**Figure 3. Prevalence of telehealth use by insurance type**

MedAdv indicates Medicare Advantage; MedSupp, Medicare Supplement; TH, telehealth.

**Figure 4. Prevalence of audio-only telehealth by insurance type**

MedAdv indicates Medicare Advantage; MedSupp, Medicare Supplement; TH, telehealth.

### Limitations

Certain limitations apply to our analysis. While we created and refined the TH definition in collaboration with a large national payer, we did not conduct benchmarking against external data (e.g., medical records). All findings should be interpreted considering the caveats commonly associated with administrative claims database analyses, including potential coding errors and incomplete data. Lastly, our analysis was conducted in a US population with commercial and Medicare Advantage/Supplement health insurance coverage, which could limit the generalizability of the results to those with other types of insurance such as traditional fee-for-service Medicare or Medicaid, none, or a population outside the United States.

### Conclusions

We created a standardized definition to identify outpatient TH using claims data, accounting for coding practices through the end of 2022. Consistent with

prior reports, TH utilization increased substantially following onset of the COVID-19 pandemic in conjunction with increased coverage and reimbursement for the service. Utilization then decreased but remains noticeably higher than before March 2020. Incorporation of TH utilization via a broad standardized definition is an essential tool for all health economic and outcomes research studies evaluating time periods from 2020 and beyond.

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## Sourcing Real-World Data for Research

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This article defines the landscape of real-world data sources that are commonly used by researchers conducting evidence-based analytics. The landscape is broadly segmented into 2 groups: (1) data from entities involved with the delivery of care (“primary stakeholder”) and (2) data from commercial entities (“secondary stakeholder”).

This article also discusses the differences, advantages, and disadvantages between data from primary stakeholders and secondary stakeholders. These differences are important considerations when selecting a data source for research analytics.

This article also defines and contrasts different types of commercial data organizations including commercial patient registries, data vendors, and data marketplaces. The differences between these organizations play a significant role in the selection of data organizations to work with on research analytics.

### Introduction

Demand for data in healthcare is at an unprecedented level. Pharmaceutical and biotechnology companies, in particular, have increased their focus on nonclinical trial data, or real-world data (RWD), to strengthen operations. Research estimates that an average large pharmaceutical company can save \$300 million by adopting real-world evidence (RWE) analytics across its whole value chain.<sup>1</sup> Every major drug company has a department focused on the use of healthcare data across multiple diseases as a result.<sup>2</sup> These departments solidified the industries’ initial interest in using healthcare data for operations into a steadfast practice.

**Research estimates that an average large pharmaceutical company can save \$300 million by adopting real-world evidence analytics across its whole value chain.**

Fortunately, healthcare is a data-rich industry. The US healthcare system is estimated to have created a total of 2314 exabytes of data in 2020.<sup>3</sup> This translates to approximately 30% of the world’s data by volume. By 2025, the compound annual growth rate of data for healthcare will reach 36%. For context, that’s 6% faster than manufacturing, 10% faster than financial services, and 11% faster than media and entertainment.<sup>4</sup>

And now healthcare data are more accessible than ever before. The historical barriers that created silos (eg, limited incentives to share, security and privacy concerns, technical inconsistencies to name a few) have largely been reduced either through federal legislation or technological advances. One of the most evident examples is the ONC Final Rule of the Cures Act (2016) that mandates the adoption of standardized application programming interfaces (APIs) to allow individuals access to structured electronic health information using

smartphone applications. It also includes a requirement that patients can access all of their electronic health information, structured or unstructured, at no cost.<sup>5</sup> This is not to say that accessing healthcare data is easy, it’s just easier.

Choosing the right data sources is critical to avoid wasted time and money on RWD projects. This article focuses on RWD which, as defined by the US Food and Drug Administration, means healthcare information derived from multiple sources outside of typical clinical research settings, including electronic medical records (EMRs), claims and billing data, product and disease registries, and patient-generated data gathered by personal devices and health applications.<sup>6</sup> More specifically, this article summarizes the pros and cons of 2 types of RWD sources: (1) data from entities involved with the delivery of care (“primary stakeholder”), and (2) data from commercial entities (“secondary stakeholder”).

### “Primary Stakeholder” Data

Primary stakeholder data sources are the local data stores for those that create healthcare data including providers, labs, insurance companies, and patients. The data storage systems they use are EHRs for clinical data, picture archiving and communication system (PACS) for images, lab information systems for lab data, claims databases for claims, and others (**Table**).

**By 2025, the compound annual growth rate of data for healthcare will reach 36%—that’s 6% faster than manufacturing, 10% faster than financial services, and 11% faster than media and entertainment.**

Primary stakeholder data sources are regarded as the source of truth in healthcare even though they are not always accurate and frequently

**Table. Data Storage Systems in Healthcare**

DATA TYPE	DATA STORAGE SYSTEM	LOCATIONS
Clinical	Electronic Health Record (EHR)	Hospitals, clinics, surgery centers
Claims	Claims Databases	Payers, hospitals, clinics
Images	Picture Archiving and Communication System (PACS)/ Vendor Neutral Archive (VNA)	Hospitals, clinics, imaging centers
Lab	Laboratory Information System (LIS)	Hospitals, clinics, labs
Pharmacy	Pharmacy, Specialty HUB	Pharmacies, specialty pharmacies, HUBs
Social Determinants of Health	Various	Wearables, employers, various
Patient Reported Outcomes	Various	Wearables, application developer databases
Clinical Trials	Electronic Data Capture (EDC)	Hospitals, clinics

Source: Advanced Data Sciences proprietary research

incomplete. They are regarded this way because the creators of these data are delivering care to the patients whether that means treatment, diagnosis, or billing. Additionally, the union of all primary stakeholder data sources is the most comprehensive view of the patient that the healthcare system currently offers. Primary stakeholder data sources represent the greatest opportunity for volume and detail that can, in theory, be used by any type of query whether it's broad or narrow in scope.

Sourcing data from primary stakeholder data sources is therefore good for highly customized data pulls. And since it connects to the same systems that providers use, bidirectional integrations to primary stakeholder sources also offer the opportunity to integrate into workflows and audit source files. These types of connections are not uncommon. Mayo Clinic as of 2020 had licensed access to its de-identified patient data to 16 companies as just one example.<sup>7</sup>

That being said, working with primary stakeholder sources can be difficult and time-consuming. Covered entities are generally careful about sharing patient data even though an increasing number are doing so. The security, privacy, and technical liabilities that come with taking ownership of the agreement, and technical implementation challenges, are not to be underestimated.

Additionally, primary stakeholder data can be extraordinarily heterogeneous and unstructured. Institutions, clinics, and other types of care settings frequently adhere to different data standards diluting the benefit of any single standard. And it is estimated that the vast majority of primary stakeholder data are unstructured creating a barrier to syntactic and semantic interoperability.<sup>8</sup>

### Secondary Stakeholder Data

Secondary stakeholder data sources are third parties that aggregate data, or the permissions for the data, and license, or grant, access to a consumer. Secondary stakeholder sources fall into

3 categories (**Figure 1**):

- Commercial patient registries
- Data vendors
- Data marketplaces

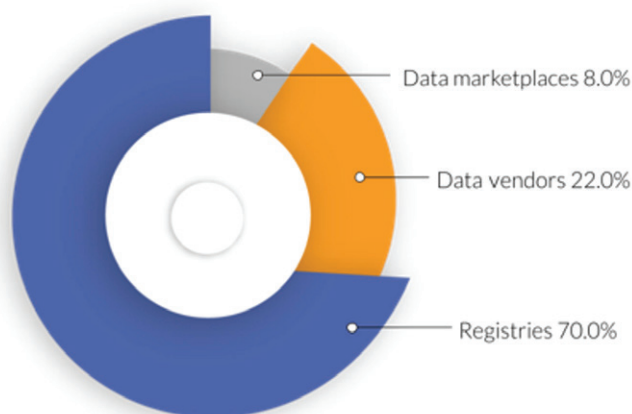
### Commercial Patient Registries

Patient registries created from EHR integrations have been around for a long time; however, they have gained considerable scale over the past 20 years. Specialty societies, academic centers, government agencies, and patient advocacy groups have led the initiative to aggregate patient data for research purposes, and to provide access for a fee. There are well over 120 registries, 90% of which are offered by specialty societies.<sup>9</sup> The registries aggregate data from many different sources, usually EHRs, to create a specialized database for a particular specialty, therapeutic area, indication, or patient profile. The size of these registries ranges from a few patients to tens of millions of patients, and not all are commercial. Examples of specialty society registries that have been commercialized include the American Academy of Ophthalmology's (AAO) IRIS,<sup>10</sup> American College of Cardiology's (ACC) and Veradigm's Cardiology Registry (formerly PINNACLE),<sup>11</sup> and the American Society of Clinical Oncology's (ASCO) CancerLinQ, among others.<sup>12</sup>

Registries are good for retrospective research on specific patient populations or therapeutic areas. In general, these registries are used only for research and not for commercial purposes. There are exceptions, such as when the registry sponsor partners with a for-profit data analytics company to prepare the data for commercial research projects. Verana Health is a good example of a 'public-private partnership' where several nonprofit specialty societies (AAO, AAN, and AUA) work with Verana Health to curate and commercialize the data in their registries.

The disadvantages of registries are that the consumer has very little control over the content

**Figure 1. Primary stakeholder data source share by organization type**



Source: Advanced Data Sciences industry research database

and curation strategies. Additionally, registries are not always open to the public. Historically they have been used for noncommercial research rather than commercial initiatives, and some maintain that approach. [The National Amyotrophic Lateral Sclerosis Registry](#), for example, reviews applications and permits only organizations that attest that the use of the data is aligned with the society's mission.

**Demand for healthcare data is increasing as access gets easier. The chief ramification of this change is that organizations across the healthcare industry can now create and implement a “healthcare data strategy.”**

#### Data Vendors

Increasingly both for-profit and nonprofit organizations are aggregating data from various healthcare settings including health systems, claims clearinghouses, and labs for commercial purposes. These data are de-identified to comply with Health Insurance Portability and Accountability Act (HIPAA) and offer some of the largest datasets available as they are able to combine single data types across many locations. Examples of data vendors include Definitive Healthcare, Clarify Health, and IQVIA for claims data; Concert.AI, Flatiron Health, and others for clinical data.

Data vendors are an efficient data source for retrospective analyses of reasonably well-normalized datasets. The advantage of working with data vendors is that they bring together many disparate data sources to a common database and typically have something for everyone. Replicating their scale and heterogeneity is oftentimes insurmountable in comparison to a home-grown initiative. They are commercial enterprises, which typically (but not always) means they move quickly to work with data consumers.

The disadvantages to working with a data vendor are that the consumer has very little control over which data are

collected, how they are pooled with other data, the ability to audit the data at the source, and there are no workflow integrations with the data sources. Additionally, the costs tend to be very high (**Figure 2**).

#### Data Marketplaces

Marketplaces are essentially brokers connecting buyers and sellers of data. These companies aggregate both supply and demand for the data and make the connection. Examples here include HealthVerity, Veradigm (an affiliate of multiple EHR companies), and Prognos Health. The benefit to these marketplaces is that they offer consumers a relatively fast (although not inexpensive) way to purchase de-identified data, and also a way for sellers to monetize their data assets. They are good for retrospective analysis of reasonably well-normalized and curated datasets.

Marketplaces are a good source of data when speed is a priority. These datasets may be similarly broad compared to data vendors and also ready for an initial analysis through a web portal. This means that analytics can start almost immediately (which in healthcare means a few days or weeks to secure data privacy permissions).

What you get in speed can lead to deficiencies in detail. Many of the data marketplace datasets are what-you-see-is-what-you-get. There is essentially no backward compatibility or ability to integrate into provider workflows. This

means that retrospective data that needs to be accessed quickly is a good fit for data marketplaces.

#### Ramifications

Demand for healthcare data is increasing as access gets easier. The chief ramification of this change is that organizations across the healthcare industry can now create and implement a “healthcare data strategy.” A “healthcare data strategy” sets the plan for any organization to include empirical evidence to improve the development and launch of products and services to care for patients.

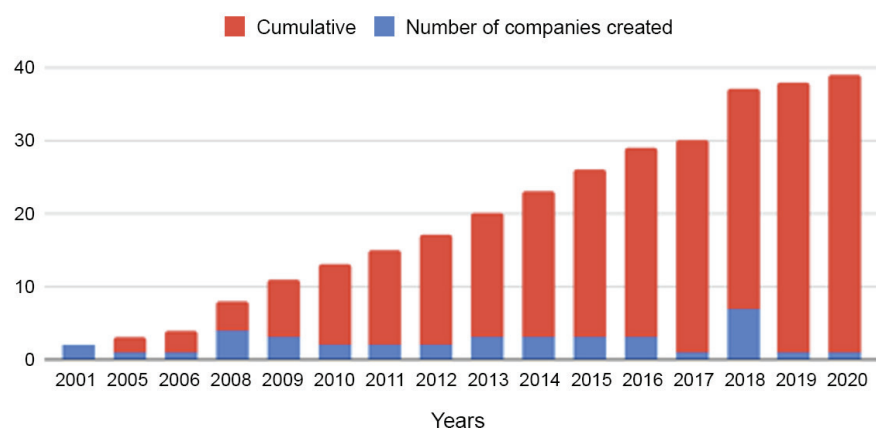
Choosing the right data source and sourcing technology efficiently are paramount when crafting a healthcare data strategy. Key considerations such as data type, quality, latency, and functionality will affect one's ability to use healthcare data for an organization's objectives. Each variable brings its own advantages and disadvantages, many of which can be analyzed prospectively.

Now there are many reliable options—and more on the way—setting the stage for an exciting new era for the biopharma industry.

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**Figure 2. Healthcare data company formations (cumulative and absolute)**



Source: *Advanced Data Sciences industry research database*

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# The Use of Item Banks in Rare Disease Clinical Trials: A Look at the Patient-Reported Outcomes Measurement Information System (PROMIS)

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A 2017 ISPOR emerging good practices report suggested that in rare disease clinical trials, the use of item banks to assess patient-reported outcomes should be considered.

This research examined the use of Patient-Reported Outcomes Measurement Information System (PROMIS) measures in rare disease clinical trials.

Overall, 20% of trials utilized item banks with a small increase observed in computer adaptive test usage in trials that began after the release of the ISPOR report.

## Introduction

When designing clinical trials for a rare disease, an important consideration is that the outcomes are clinically relevant and interpretable.<sup>1</sup> This consideration should be applied not only to clinical outcomes but also to patient-reported outcomes (PROs) that evaluate health-related quality of life (HRQoL). However, there are challenges with PRO assessment in rare disease clinical trials.<sup>2</sup>

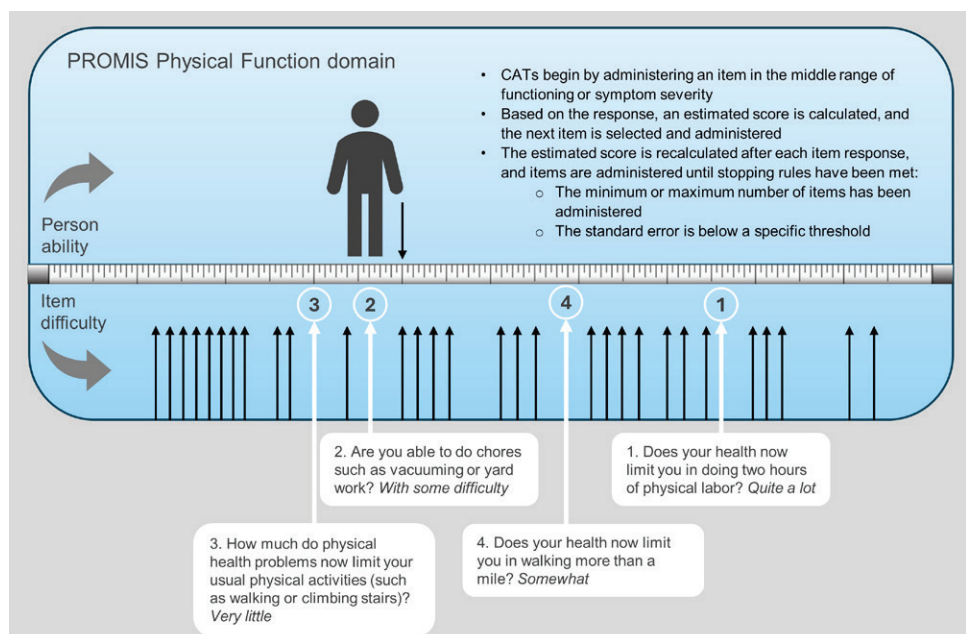
An ISPOR emerging good practices report was published in 2017 that specifically addressed PRO assessment in rare disease clinical trials.<sup>2</sup> The report stated that the main challenges associated with PRO measure selection in rare disease research include limited availability of disease-specific PRO measures and substantial heterogeneity in symptoms between patients with a rare disease, thereby impacting the ability to measure outcomes across the entire spectrum of the disease.<sup>2</sup> One solution that could address both challenges is to consider using item banks, such as the Patient-Reported Outcomes Measurement

Information System (PROMIS), because they allow for the selection of the most appropriate items for patients.<sup>2</sup>

PROMIS measures can be administered in various formats. A format commonly used is the short form, a fixed-length measure in which all respondents complete the same items.<sup>3</sup> Examples of PROMIS short forms include traditional short forms, profiles (eg, PROMIS-29, PROMIS-37), and the 10-item global health scale. Alternatively, PROMIS measures can be administered using item banks, a collection of items all measuring the same construct (eg, physical function). Item banks allow for customization for a specific patient population in the form of a computer adaptive test (CAT) (Figure 1) or the development of a custom short form.<sup>4,5</sup>

Custom short forms can use any items in the item bank, with patients, clinicians, and researchers selecting items with the most relevant content, and psychometricians validating the new measure.<sup>5</sup> CATs can also use any

Figure 1. PROMIS CAT simulated administration



CAT indicates computer adaptive test; PROMIS, Patient-Reported Outcomes Measurement Information System. Source: CAT administration information from HealthMeasures<sup>4</sup>; figure adapted from Tulskey, et al.<sup>11</sup>

items in the item bank. Utilizing item response theory, the selection of items is tailored for each respondent, ensuring high measurement precision across the spectrum of functioning and symptom severity within a patient population. Thus, CATs are brief, precise, and relevant to the respondent.<sup>3,4</sup>

One key difference between administering short forms and administering item banks such as CATs pertains to measurement precision. The degree of measurement precision with short forms is variable,<sup>3</sup> potentially reducing their clinical relevance and interpretability. CATs offer a wider range of accurate scores and are less affected by floor and ceiling effects.<sup>6</sup> Floor and ceiling effects refer to instances when >15% of respondents have the lowest or highest possible score, respectively. The presence of floor or ceiling effects suggests that items are missing at the lowest or highest ends of the PRO measure, thereby affecting reliability and validity.<sup>7</sup> It is recommended that CATs be used over short forms when the patient population is in very poor health and when it is necessary to administer a smaller number of items.<sup>6</sup> Both of these factors are important considerations when conducting rare disease clinical research.

## When designing clinical trials for a rare disease, an important consideration is that the outcomes are clinically relevant and interpretable.

With the solution suggested by the 2017 ISPOR report in mind, our objective was to review publications since 2017 to explore how PROMIS measures have been utilized in rare disease clinical trials with a specific focus on the use of PROMIS item banks compared with the use of PROMIS short forms.

### What we found

PubMed was searched using the terms “patient-reported outcomes measurement information system,” “PROMIS,” and “clinical trial” for studies published between 2017 and 2022 describing rare disease clinical trials

that included PROMIS measures as an outcome. The identified studies were reviewed independently by 2 of the authors, and data were extracted regarding which PROMIS measures were included as trial outcomes, how these measures were administered, and when the trial began (ie, before or after the July/August 2017 publication date of the ISPOR report). In addition, [www.clinicaltrials.gov](http://www.clinicaltrials.gov) was searched to determine if any PROMIS publications that were automatically indexed to rare disease clinical trials had not been identified through the PubMed search.

Our search yielded 36 relevant articles reporting on 30 different rare disease clinical trials. Although some clinical trials administered more than one type of PROMIS measure, the majority (80%) used only fixed-length short forms. Only 20% of trials utilized PROMIS item banks. Specifically, PROMIS CATs were administered in 4 trials, and in 2 trials, custom short forms were created for specific patient populations (eg, tenosynovial giant cell tumor, X-linked hypophosphatemia). In comparing trials that began before and after the publication of the ISPOR emerging good practices report, a small increase was observed in the proportion of PROMIS measures administered as CATs (**Figure 2**).

Regarding the use of item banks in 6 of the 30 rare disease clinical trials, we took a closer look at what domains were assessed. The PROMIS domains administered via CATs illustrate the broad spectrum of HRQoL assessed in these rare disease clinical trials, including fatigue, physical function, pain interference, mobility, sleep disturbance, cognitive function, anxiety, depression, anger, peer relations, and ability to participate in social roles and activities. Of the 4 trials that administered PROMIS CATs, half also utilized the PROMIS 10-item global health scale, a

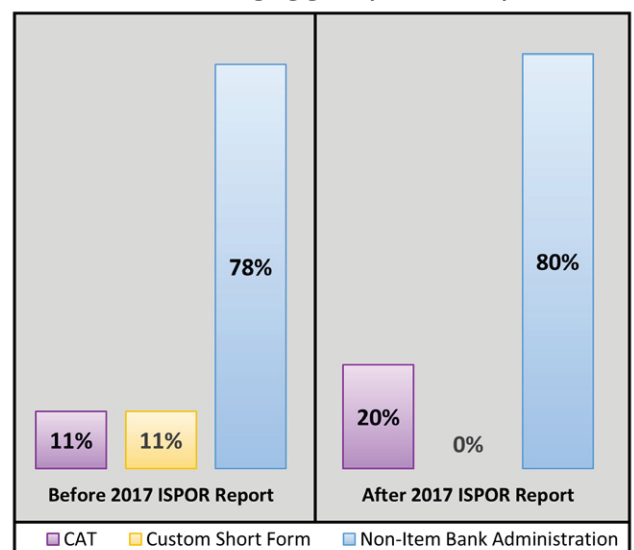
fixed-length short form that broadly assesses HRQoL. The 2 trials that utilized item banks to develop custom short forms focused primarily on assessing the physical health dimension of HRQoL (eg, fatigue, physical function, pain interference).

Establishing the value of a drug for a rare disease is difficult as traditional methods that focus on cost-effectiveness do not fully account for other factors such as the increased severity of the disease, the social value placed on incremental improvements in outcomes, and the lack of alternative treatment options.

### Strengths and Limitations

This research is an early look at the impact of the 2017 ISPOR emerging good practices report. One of the purposes of the report was to recommend solutions that would increase PRO measure usage in rare disease clinical trials, thereby enhancing our understanding of treatment benefits from the patient's perspective. We found that PROMIS item

**Figure 2. PROMIS use before and after the release of the 2017 ISPOR emerging good practices report**



CAT indicates computer adaptive test; PROMIS, Patient-Reported Outcomes Measurement Information System.

banks have been used in rare disease clinical trials, suggesting that this is a feasible option that may be on the rise. Of the 4 trials that administered PROMIS CATs, multiple CATs were utilized across various domains of HRQoL, gathering a substantial amount of information while keeping patient burden low. Additionally, our findings are consistent with other research showing that the use of CATs in clinical trials, in general, may be increasing over time.<sup>8</sup>

The primary limitation of this research is that only published studies were examined. Our findings may not reflect the full picture of PROMIS utilization in rare disease clinical research because the publication of PRO results from clinical trials is often delayed or results are not published at all. It is critical that PRO results be included in peer-reviewed publications, and ideally reported with a trial's primary endpoints as opposed to being reserved for a separate, later publication. Specifically, it is recommended that researchers make use of the consolidated standards

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of reporting trials (CONSORT) PRO extension guidelines.<sup>9</sup> This will allow for greater dissemination of PRO findings to patients and clinicians, thereby facilitating shared decision making. Another limitation is that our observation period from 2017 to 2022 may have been too short to detect changes in PRO measure administration and too early to witness the potential adoption of ISPOR recommendations made in 2017.

### Conclusions

PROMIS item banks have been utilized in rare disease clinical trials both before and after the release of the 2017 ISPOR

emerging good practices report, with a small increase in the proportion of PROMIS measures administered as CATs since the report was published. However, the primary mode of PROMIS administration remains the use of fixed-length short forms.

**Increased use of PROMIS item banks will enhance our understanding of health-related quality of life among patients with rare diseases.**

Challenges faced when trialing a new treatment for a rare disease have implications in subsequent health technology assessments to determine value and, ultimately, patient access.<sup>10</sup> Establishing the value of a drug for a rare disease is difficult because traditional methods that focus on cost-effectiveness do not fully account for other factors such as the increased severity of the disease, the social value placed on incremental improvements in outcomes, and the lack of alternative treatment options.<sup>10</sup> Health technology assessment agencies are modifying their methods for the evaluation of treatments for rare diseases, with the impact on HRQoL an important consideration for some.<sup>10</sup>

Over time, increased use of PROMIS item banks will enhance our understanding of HRQoL among patients with rare diseases by providing more sensitive measurement of HRQoL while also reducing patient burden. Any improvement to the quality and precision of PRO inputs using PROMIS item banks that feed into health technology assessment will result in a more informed decision on the value of the treatment for patients and payers.

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