

VALUE & OUTCOMES SPOTLIGHT

A magazine for the global HEOR community.

Including Patients as Partners in Clinical and Outcomes Research



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Improving healthcare decisions

VALUE & OUTCOMES SPOTLIGHT

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

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FROM THE EDITOR

The Power of the Patient

Patient centricity and patient engagement in clinical and health economics and outcomes research (HEOR) is a key component of value-based healthcare, which focuses on improving the quality of care, while reducing costs. In the past, patients were passive recipients of healthcare; today they are active participants. With a multitude of available resources, patients and caregivers have become more educated about, more engaged in, and more empowered in their choices over their own healthcare and treatment. Patients want to partner, engage, and work with their healthcare providers to have access to the best treatments and maximize outcomes to improve their lives in ways that are more meaningful to them.

Patient voices matter. We should not underestimate the power of the patient. Through meaningful partnerships with patients, patient advocacy groups, patient influencers, and caregivers, we can gain significant patient insights and knowledge to build a foundation from clinical trial design to lifecycle management and execution of innovative treatments. These partnerships could also guide future research and development and provide

**In the past, patients
were passive recipients
of healthcare; today they
are active participants.**

clinical and real-world evidence to inform decisions of healthcare leaders, researchers, manufacturers, payers, and policy makers. By demonstrating patient value, we will be able to provide a holistic approach and personalized patient solutions to improve patient outcomes.

To achieve patient centricity, we must listen to patients, understand their patient journeys and their experiences, have continuous dialogue with them

and their caregivers to really understand what they face and find solutions that matter most to them. This involves incorporation of patient perspectives across the full care spectrum, including clinical and outcomes research, lifecycle of the drug development process, shared healthcare decision making, patient outcomes measures, and how value is defined through their lens.

Best practices in conducting patient-centric research include engaging patients in the research process, collecting data on the patient's experience, and using patient-centered outcomes. Collecting data on the patient's experience can help to identify areas where improvements can be made. This could include things like dietary changes, exercise programs, or mental health support. By addressing these issues, healthcare providers can improve patient outcomes and help patients to live healthier lives.

Patient-centered clinical trials and outcomes research are critical to improving healthcare. These trials focus on the patient experience and aim to improve patient outcomes by taking into account the patient's perspective. These are designed to be more inclusive to better reflect the diversity of patients, be more flexible by allowing for changes to be made based on patient feedback, and they can help to improve patient engagement. By involving patients in the design and implementation of clinical trials throughout the lifecycle of the drug development process, healthcare providers and researchers can ensure that the trials are more relevant to the patient's experience. This can help to improve patient outcomes, increase patient satisfaction with the healthcare system, and improve adherence and persistence. When patients are engaged and invest in their own health, we see better patient outcomes.

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patient outcomes.**

Patient centricity in HEOR can be facilitated by the collaboration of patients, payers, manufacturers, health technology assessment (HTA) agencies, and HEOR professionals. Patients can provide valuable insights into their experiences with healthcare, which can help to inform the development of patient-centered outcomes. Payers can help to ensure that healthcare is accessible and affordable for patients. Manufacturers can develop products that are tailored to the needs of patients. HTA agencies can use real-world evidence to make more informed decisions about patient care. HEOR professionals can help to identify areas where improvements can be made to patient outcomes. By working together, we can help to improve patient outcomes and promote patient-centric healthcare.

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



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

FROM THE CEO

Putting Patients at the Center of Health Economics and Outcomes Research

Rob Abbott, CEO and Executive Director, ISPOR

Health economics and outcomes research (HEOR) is, by definition, a multidisciplinary and multifaceted endeavor. As such, it is sometimes easy to get “lost” in the nuance of a particular cost-effectiveness study or the latest debates about quality-adjusted life years. If one takes a metaphorical step back, though, and thinks about the end rather than the means to get there, it’s much easier to navigate our field. To borrow from the political strategist, James Carville, “it’s about the patient, stupid.”

Everything we do is ultimately about making healthcare systems more accessible, more equitable, and more impactful for patients. It’s really that simple—not easy, but simple.

All of us have been, or will be, patients. And we certainly know family members and friends who have been patients. We have skin in this game and should care in a very personal way about the level of engagement and the level of care that is accorded to patients. Looking forward, it also seems clear that enabling and empowering patients to practice better “self-care” will be an increasingly important feature of the healthcare landscape. To get there, we need to better understand—and value—the things that matter to patients; the things that actually make a difference to their health and enable them to enrich their experience of life.

This is something that ISPOR takes very seriously. We think of patient-centered work as the “active, meaningful, and collaborative interaction between patients and researchers across all stages of the research process, where research decision making is guided by patients’ contributions as partners, recognizing their specific experiences, values, and expertise.” To me, this is nothing less than getting real about what we’re doing as HEOR scholars, practitioners, or advocates and ensuring that in our quest for “understanding” we don’t get lost in data and rush past the reason we gathered that data in the first place—to help a patient. It’s also about taking the steps to ensure that

Everything we do is ultimately about making healthcare systems more accessible, more equitable, and more impactful for patients.

we are actively creating the conditions in which patients, their caregivers, and their families are able to grow their knowledge and develop the skills and confidence to more effectively manage and make informed decisions about their own health and healthcare. At the risk of stating the obvious, this is not a “one-size-fits-all” proposition. It needs to be coordinated and tailored to the unique needs of each patient. This is why our

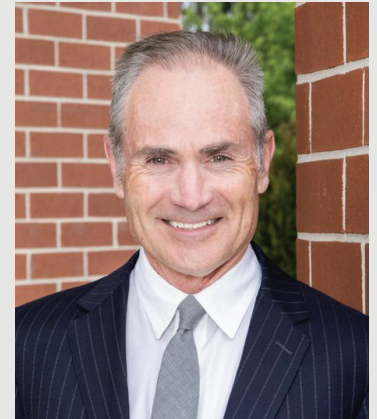
commitment to patient-centered outcomes research is so important; it helps people and their caregivers communicate and make informed healthcare decisions, allowing their voices to be heard in assessing the value—to them—of different healthcare options.

A lot of progress has been made in putting patients at the center of HEOR, and we are still a long way from where we need and want to be. Anyone who works in healthcare globally would agree, I think, that amplifying the patient voice and creating a more patient-centric decision-making process is a necessity, but also recognize that challenges remain in terms of bringing in the patient across the entire healthcare journey.

Everything we do is intended to enhance people’s health in the first instance, and make the patient experience better when one’s health has been compromised.

ISPOR has worked hard to elevate the patient voice in our work, and it is one of my personal areas of focus as CEO. I am pleased to say that we have [patient councils and roundtables](#) that meet regularly and draw from patient representatives from around the globe. For those coming from low- and middle-income countries, we provide [travel grants](#) and fee waivers to ensure that they can participate and bring their diverse perspectives to bear. We also have a [special interest group](#) centered exclusively on leveraging the patient experience to inform our recommendations. In 2024, we will be upping the ante, so to speak, and bringing patients together for a global summit that allows for even greater interaction and shared learning.

As we embark on a new strategy for ISPOR in 2024, our society will be more actively working to position HEOR as a key tool to address the biggest challenges in healthcare globally: affordability, the impact of accelerating digitalization of health, and the growing interest in whole health. At the center of each of these challenges, however, is the patient. It bears repeating: everything we do is intended to enhance people’s health in the first instance, and make the patient experience better when one’s health has been compromised. I invite you to join us in making this a reality.



RECORD-BREAKING ATTENDANCE AT ISPOR EUROPE 2023

The ISPOR Europe 2023 conference lived up to its description as a “must-attend event,” as it hosted 5600+ attendees in Copenhagen, Denmark on November 12-15, 2023. The conference theme, “HEOR at the Nexus of Policy and Science,” explored how healthcare policy is evolving rapidly to address issues around the use of real-world evidence, cross-border collaboration, affordability, and equity.

Hopefully, the photos below capture some of the energy and excitement from the event. For more news and photos from the conference, visit [ISPOR's HEOR News Center](#).







ISPOR NEWS

The ISPOR HEOR Competencies Framework™: Updates Underway

Annesha White, PharmD, PhD, University of North Texas, Forth Worth, TX, USA; Soham Shukla, PharmD, MS, GSK, Collegeville, PA, USA

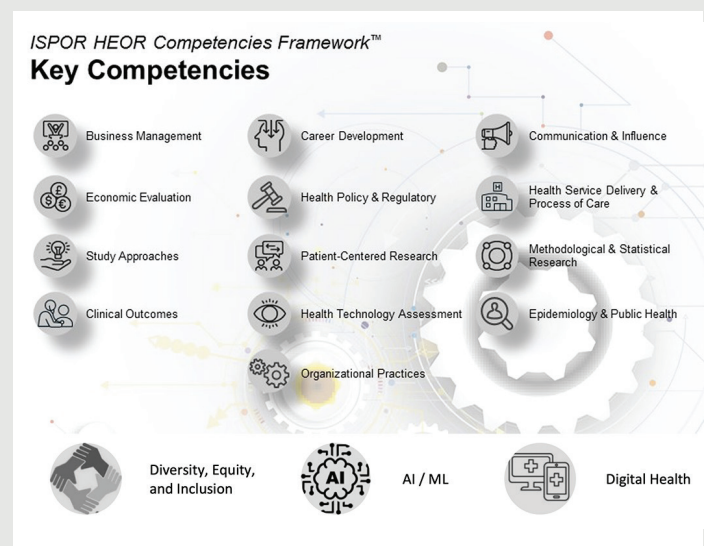
The discipline of health economics and outcomes research (HEOR) has evolved over time with many advances in the field that reflect the need for uniquely skilled professionals to create, implement, and evaluate the different aspects of HEOR. Core competencies are an essential prerequisite for establishing HEOR as a professional discipline. Competencies refer to the technical, social and ethical, and personal and professional skills needed to develop a capable HEOR workforce. Competencies may serve as a guide for professionals on the knowledge, attitudes, and behaviors needed to perform effectively in the HEOR discipline. Competencies can also serve to help identify strategies for career growth while pointing professionals towards development opportunities for the future.

In 2020, the creation of a set of competencies for HEOR leveraged the expertise and perspectives of ISPOR members through a collaboration between ISPOR's Institutional Council and Faculty Advisor Council to identify and validate the ISPOR HEOR Competencies Framework (CF).¹ The process included natural language processing to examine competencies included in ISPOR Career Center HEOR job postings, qualitative input from a focused Institutional Council–Faculty Advisor Council work group, and quantitative input from 3 surveys: (1) a general member survey to assess importance and relevance of each competency, (2) a faculty member survey to assess the extent to which HEOR graduate degree programs cover the competencies, and (3) a student member survey to assess exposure to the competencies. Beth Devine, PhD, a member of ISPOR's board of directors, commented, "Our field is so broad and vast that there is a need to establish focus and benchmarks for competencies in each subfield of HEOR. Because our field is evolving so rapidly, there are many uses for the Framework: to guide curriculum in academic programs as they are continually updated, to inform lifelong learning topics for all HEOR professionals, and to assist hiring managers to set benchmarks for competency in employment opportunities."

As the HEOR field advances, so do the job types and the breadth of topics in which professionals must demonstrate competence. Therefore, updates to the CF are necessary to ensure their currency and comprehensiveness. Jim Murray, PhD, a co-chair of the original work group, commented, "HEOR has evolved into its own unique discipline separate from its foundations (eg, health systems research). It is a complex discipline comprised of many different competencies that have not been previously defined. The ISPOR Competency Framework is intended to not only define the HEOR competencies but also to identify the skills and experience needed for practitioners in the HEOR field."

In the current CF, there are 41 competencies organized into 13 key competency domains. Three additional topics will be added in this update (Figure).

Figure 1. Competency Domains and New Topics



The process to update the CF involved convening a 10-member diverse group of HEOR representatives to comprise a work group charged with systematically reviewing the existing competencies, suggesting new competencies, and reducing the number of targeted competencies for this update. A 15-member review team of experts in the HEOR field was also brought together to provide additional input, review, and feedback. Meetings before, during, and after the 2023 ISPOR annual conference revealed some similarities in HEOR responsibilities of the past, but also some contemporary differences that signal an evolution of the profession.

• **Diversity, Equity, and Inclusion (DEI):** Although building competence in DEI is a journey and not a destination, this work provides a standard set of expectations or outcomes. These DEI competencies relate to data collection, systems-level changes, advocacy, policy changes, and role modeling to incorporate into local environments, education, and training. Work group member Eberechukwu Onukwugha, MSc, PhD commented, "As with many STEM (science, technology, engineering, math) fields, there is a need for greater diversity and representation across the continuum of education, training, employment, and leadership opportunities in the HEOR field. Diversity of thought and perspectives enriches our classrooms, collaborations, meeting spaces, and boardrooms. Inclusion of DEI principles within the HEOR competency framework acknowledges the work on disparities, access, and healthcare delivery that has been conducted to date by HEOR professionals worldwide and lays the groundwork for future innovations in how we design, conduct, and amplify HEOR."

• **Artificial Intelligence/Machine Learning (AI/ML):** AI refers to the broader field of creating systems/services that can perform tasks that typically require human intelligence. ML is a subset of AI, representing a family of statistical methods that focuses on data regression, classification, ranking, and prediction. As modern healthcare data have massive volume, rapid turnover, and complex multidimensional structures, they require efficient methods to generate evidence where traditional approaches are limited or costly. Work group member Katarzyna Wac recently commented on the growing importance of this competency, “HEOR professionals need skills to manage the exponential growth of the AI-based approaches to understand how the evidence was derived and how to systematically approach the growing use of machine learning in the field.”

• **Digital Health:** The term “digital health” is broad and can include electronic medical/health records, telemedicine, mobile health, and wireless health. Utilization of digital health technologies provides opportunities to increase the quality of care and accuracy of healthcare analytics, and ensures greater safety for the patient.

• **Statistics and Analytics:** This area exists in the current Framework as a single competency under its own domain. However, given its broad scope and importance/relevance to HEOR, it will be expanded upon in the update into multiple specific competencies based on a separate project to identify topics in statistics and analytics led by Onukwugha and colleagues.

As an outcome, the complete update of the CF will be published and available on the ISPOR website in 2024. A draft of the updated CF is complete and ready to be vetted via an ISPOR general member survey. The general member survey will be administered to the ISPOR membership at large, including

faculty and students, to obtain members’ opinions on (1) the importance of each competency to the overall HEOR discipline, and 2) the relevance of each competency to the specific job held by the respondent. Future plans include promoting the use of the competencies among researchers, academicians, practitioners, and the next generation of HEOR professionals. To this end, the work group launched the updated competency framework general survey in September 2023 to reverify the relevance and importance of each competency and subcompetency. In addition, comments were sought during the 2023 ISPOR Europe conference. After soliciting external reviews/comments and critically analyzing the feedback, recommendations will be finalized.

Please reach out to the ISPOR work group co-chairs Annesha White (annesha.white@unthsc.edu) and Soham Shukla (soham.h.shukla@gsk.com) with any questions or feedback.

Reference:

1. Pizzi L, Onukwugha E, Corey R, et al. Competencies for professionals in health economics and outcomes research: The ISPOR Health Economics and Outcomes Research Competencies Framework. *Value Health*. 2020;23(9):1120-1127. doi: 10.1016/j.jval.2020.04.1834

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HEOR NEWS

1 Confronting High Costs and Clinical Uncertainty: Innovative Payment Models for Gene Therapies

(Health Affairs)

In looking at how to pay for expensive gene therapies, researchers developed a taxonomy of possible payment mechanisms, including installments, risk pools, reinsurance, price-volume agreements, expenditure caps, subscriptions, outcomes-based payments and rebates, warranties, population outcomes-based agreements, and coverage with evidence development. The researchers then discuss each payment model, its advantages and challenges, and considerations for US payers.

[Read more](#)**2 A Systematic Review of COVID-19 Misinformation Interventions: Lessons Learned**

(Health Affairs)

Researchers looked at 50 papers evaluating the effectiveness of misinformation interventions by governments, public health authorities, and social media platforms during the COVID-19 pandemic and conclude that more public health experts need to be included in intervention design and to develop a health misinformation typology; agreed-upon outcome measures; and more global, more longitudinal, more video-based, and more platform-diverse studies.

[Read more](#)**3 Can Postmarket Evidence Generation Be Streamlined? FDA-Commissioned Report Proposes Solutions**

(Endpoints News)

The Reagan-Udall Foundation says the US Food and Drug Administration's (FDA) postmarket evidence-generation system is too complicated and expensive. The foundation is recommending that the FDA lead an interagency task force, composed of members from the National Institutes of Health, Centers for Medicare & Medicaid Services, and the Office of the National Coordinator for Health Information Technology to establish guidelines for postmarket evidence-generation standards.

[Read more](#)**4 A Third of Nurses Report Witnessing Patients Die Due to Staff Shortages, New Global Survey Finds**

(Euronews.next)

In a survey of 2000 healthcare workers, a third of frontline nurses have had patients die in their care due to staff shortages, and more than half of respondents said they regularly think about quitting and have raised concerns about the state of their countries' health systems.

[Read more](#)**5 2023 March of Dimes Report Card Shows Modest Improvement in US Preterm Birth Rate, Which Remains at Decade-Long High, Earning Nation D+ Grade**

(March of Dimes)

According to the 2023 report, the US preterm birth rate remains

alarmingly high with data revealing persistent racial disparities across key maternal and infant health indicators, making the United States among the most dangerous developed nations for childbirth.

[Read more](#)**6 WHO Issues New and Updated Recommendations on Treatment of Mental, Neurological, and Substance Use Conditions**

(World Health Organization)

The World Health Organization (WHO) has published the third edition of the Mental Health Gap Action Program, which includes 30 updated and 18 new recommendations related to mental, neurological, and substance use conditions, alongside 90 pre-existing recommendations.

[Read more](#)**7 NICE Draft Updated Guideline Recommends More Treatment Choices for Menopause Symptoms**

(NICE)

The organization says cognitive behavioral therapy can help reduce menopause symptoms, including hot flashes and night sweats, depressive symptoms, and problems sleeping. The new guideline also outlines the risks and benefits of hormone replacement therapy.

[Read more](#)**8 Survey Reveals Impractical Working Conditions in Healthcare Reason Behind Shortage of Staff**

(Hindustan Times)

According to the Medico Legal Society of India, an association of doctors and medico-legal experts, impractical working conditions such as inadequate staff, infrastructure, and supply of essential medicines are the prime reasons behind doctors' unwillingness to work in the public healthcare sector.

[Read more](#)**9 WHO Launches Commission to Foster Social Connection**

(World Health Organization)

WHO has announced a new Commission on Social Connection, which will analyze the central role social connection plays in improving health for people of all ages and outline solutions to build social connections at scale.

[Read more](#)**10 WHO Releases Priorities for Research and Development of Age-Appropriate Medicines for Treatment of Neglected Tropical Diseases**

(World Health Organization)

The World Health Organization (WHO) has identified priority pediatric formulations for 5 neglected tropical diseases—human African trypanosomiasis, onchocerciasis, scabies, schistosomiasis, and visceral leishmaniasis—to target research and development in addressing the specific needs of infants and children.

[Read more](#)

FROM THE JOURNALS

Care Pathway Analysis to Inform the Earliest Stages of Technology Development: Scoping Oncological Indications in Need of Innovation

Scholte M, Heidkamp J, Hannink G, Merks MAW, Grutters JPC, Rovers MM. *Value Health*. 2023;26(12):1744-1753.

Section Editor: Agnes Benedict

Many medical innovations are applicable across several disease areas. Identifying where they would make the biggest contribution to overall patient health is an important process that innovators, public and private funders of research, and payers of health services go through. The assessment process is sometimes referred to as development-focused health technology assessment, or early health technology assessment. While many organizations do this more or less transparently and explicitly in order to prioritize disease areas for products, few standardized methods have been proposed for this. An [article by Boutell et al](#) published in the *International Journal of Technology Assessment in Health Care* proposes care pathway analysis as one approach.

Care pathway analysis is a systematic process to evaluate and improve the efficiency and quality of patient care. It involves mapping out and visually presenting the sequence of events, interventions, and resources required to deliver a specific type of care or manage a particular health condition. By analyzing the care pathway, healthcare providers can identify variations in practice, potential bottlenecks, and opportunities for improvement. This analysis helps in optimizing resource allocation, reducing unnecessary costs, enhancing patient outcomes, and standardizing care delivery across different settings.

In their recent paper published in *Value in Health*, [Scholte et al](#) set out to explore a care pathway approach in the context of innovation. Specifically, their paper investigates which cancer areas would benefit most from most newly developed advanced imaging techniques that are aimed at identifying

tumor tissue and detecting positive margins during surgery (eg, optical coherence tomography). Their key outcome is an “effectiveness gap”—the difference between the ideal outcome (complete resection for all) and the status quo (with current rates of positive and negative margins). The magnitude of the effectiveness gap is then used to identify the areas that would benefit most from advanced imaging techniques.

The care pathway analysis included semistructured interviews that were conducted at multiple timepoints: before the study to find out about margin assessment and identify cancer areas where margin assessment is important; and at the results stages to externally validate the resulting pathway diagrams, data inputs, and results. A very simple general model was specified that would be applicable for each cancer area. It captured annual number of patients impacted, the groups of patients with and without complete resection, and the implications of complete versus incomplete resection, in terms of quality of life, recurrence, and 5-year overall survival. A Sankey diagram was constructed to graphically represent the pathways with several layers of information (see the example for breast cancer in **Figure 1**).

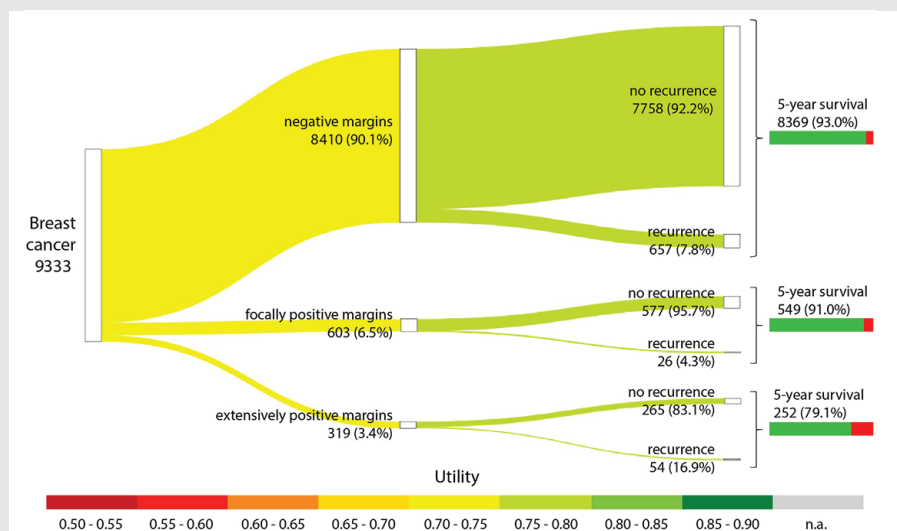
Models were parameterized based on a Dutch registry for patient numbers and surgery results, and desk research on health utilities, recurrence, and survival rates, covering 6 cancer areas: breast cancer, glioblastoma, bladder cancer, prostate cancer, pancreatic cancer, and oral cavity cancer.

The authors presented results for each cancer in terms of recurrence rates in utility values and in 5-year overall survival in a simple transparent table. Authors stopped short of creating a summary metric for the effectiveness gap and no attempt was made at analyzing uncertainty.

Nevertheless, by using a comprehensive and systematic assessment of existing care pathways with a simple model, they allow comparisons across conditions. The models are easy to update with new information or to incorporate major changes (eg, emergence of curative therapies). By comparing the effectiveness gaps, the potential for maximizing health benefits of innovative solutions can be highlighted from several perspectives.

Even with limitations, such formal exercise could provide a more informed approach to prioritize scarce research funding and investment for both public and private funders of research.

Figure 1. Care pathway analysis for breast cancer.



RESEARCH ROUNDUP

Section Editor: **Aakash Bipin Gandhi, BPharm, PhD, Methodologist Expert, RWD, Sanofi, Cambridge, MA, USA**

Enhanced patient-centricity: how the biopharmaceutical industry is optimizing patient care through AI/ML/DL.

Zou KH, Li JZ. *Healthcare*. 2022;(10;10):1997.

Summary

The study by Zou and Li discusses the application of novel methodologies based on artificial intelligence (AI), machine learning (ML), and deep learning (DL) that can be applied to real-world data to generate patient insights that can help evaluate, predict, and improve patient outcomes.

Relevance

In the absence of disease-related data during the initial stages of the pandemic, AI, ML and DL helped predict disease diagnosis based on underlying patient characteristics, chart disease trajectories, and determine prioritization of scarce resources that could be targeted towards vulnerable populations in need of care. However, pharmaceutical companies and healthcare organizations may face challenges in the adoption of these technologies for the improvement of patient-centric data generation and associated care. First, these organizations may have difficulty setting up systems and infrastructure to support large datasets and the associated computational capacity to analyze the same. Second, organizations may face challenges setting up internal standards or policies to govern real-world datasets and associated processing. Third, although real-world data can help potentiate generation of patient-centric insights through advanced analytical approaches, there is also a requirement to ensure that patient privacy is not compromised and that all necessary privacy standards are met.

A systems approach to person-centric health economics.

Kimsey L, Hoburg A, Olaiya S, Jones KD, Richard P. *Mil Med*. 2018(183;suppl 3):233-238.

Summary

The study by Kimsey et al identifies and discusses 3 approaches that can be adopted to reprioritize the nation's focus on healthcare that can deliver higher value and utility for individual health. First, the authors propose that if physician and hospital reimbursement is tied to their adoption of cost-effective therapies it could lead to incentive on the supply side of healthcare. Second, similar to pharmaceutical formularies, adopting a tiered copayment system can lead to lower copayments for patients if they decide to adopt cost-effective treatments for their disease conditions. This could, in turn, provide an incentive on the demand side of healthcare. Third, cross-pollination of information, strategies, and ideas with

other sectors can ensure that efforts are not duplicated across industries and avoid overspending of financial resources. Instead, different government agencies or business can coordinate and target their efforts in a way that encourages health-enhancing behaviors on an individual level within society.

Relevance

In the present article, the authors discuss that a general supply and demand can help explain factors involved in patient-centric health economics. Overall, the application of cost-effectiveness analysis to healthcare research questions, adopting diverse opinions and inputs across different industries and sectors, and encouraging individuals to take ownership of their health through engagement in healthy behaviors can collectively help deliver value for individual health.

Embedding patient-centricity by collaborating with patients to transform the rare disease ecosystem.

Sharma R, Ahmed S, Campagnari J, Huff W, Lloyd L. *E Pharmaceut Med*. 2023;37(4):265-273.

Summary

In this article, Sharma et al discuss a novel partnership between pharmaceutical companies and patients that provides a structured framework for understanding patient and caregiver needs and lived experiences. This partnership resulted in the creation of 2 specific design platforms geared towards this initiative on the pharmaceutical manufacturer's side. The first design platform called STAR (Solutions to Accelerate Results for patients) is aimed at generating patient insights at the global level that aid drug development and product strategies. Further, the platform also helps achieve cross-functional alignment on patient-centric matters internally within the organization and shape engagement plans on this topic with external stakeholders. The second design platform called LEAP (Learn, Evolve, Activate, and deliver for Patients) Immersive Solutions helps produce patient and stakeholder insights at a country-level, describe the patient journey and lived experiences, and support country-level drug launches based on this information.

Relevance

The creation of digital organizational tools and platforms can facilitate the involvement of patients as partners in business strategy and related solutions associated with drug development and launch activities.

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

ISPOR Conferences and Events

ISPOR 2024 | May 5-8

Georgia World Congress Center, Atlanta, Georgia, USA



Join global healthcare leaders, in person as they convene at ISPOR 2024 for discussion and dissemination of the latest topics in health economics and outcomes research (HEOR).

This must-attend event provides you with dedicated opportunities to network with your peers, HEOR experts, and thought leaders and to discuss with a global audience how we establish, incentivize, and share value sustainable for health systems, patients, and technology developers. The conference is complete with plenary sessions, spotlights, breakouts, forums, short courses, sponsored educational symposia, Exhibit Hall Theater presentations, discussion groups, poster tours and a poster hall, an exhibit hall, and more. View the [preliminary program](#).

Abstract submissions are open!

Note the dates and submit today:

	Submission Deadlines:	Notifications:
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Including Patients as Partners in Clinical and Outcomes Research



BY JOHN WATKINS, PHARMD, MPH, BCPS, MANAGED CARE PERSPECTIVES, LLC, BOTHELL, WA, USA

Patient centricity is a relatively new perspective. It's easy to regard patients as objects to be treated or problems to be fixed, rather than as people with hopes, dreams, and unique life circumstances. Patient-centered healthcare is "respectful of and responsive to individual patient preferences, needs, and values in context of their own social worlds. Patient centeredness is created by engaging, informing, and actively listening to people with chronic conditions at every point of contact."¹ Organic inclusion of patient voices in research helps develop treatments that improve their lives in ways that matter most to them. It is good economics and good policy because the patient is the ultimate judge of value. To achieve patient centricity in research requires thought and effort. Patients and caregivers must work with researchers at every stage of the process.^{2,3}

Patient-centric research processes

For results to be generalizable, researchers need a broad sample representing the heterogeneity of the patient population, but subgroups are often missed in recruiting due to logistic, financial, and/or sociocultural barriers to participation. Patients can help identify these barriers and suggest ways to improve recruitment from the overlooked groups. Patient-centered outcomes must relate to patients' experiences, perspectives, needs, and priorities. They are the ones that patients think are meaningful to them, regardless of how the data are obtained. (References to "patients" in this article include caregivers where appropriate.)

Organic inclusion of patient voices in research helps develop treatments that improve their lives in ways that matter most to them.

Patient-centric research was defined by ISPOR's Patient Engagement in Research Working Group as "the active, meaningful, and collaborative interaction between patients and researchers across all stages of the research process, where research decision making is guided by patients' contributions as partners, recognizing their specific experiences, values, and expertise."⁴ Patient-centric research identifies questions meaningful to patients, refines study designs based on their insights, and produces results that are useful in making patient-level decisions. According to research by Perfetto et al, "Patients might report that what is important to them are everyday life impacts—concepts that can be very different from the more typical clinical outcomes we often track."⁵ A parent of a teenager with muscular dystrophy commented that her son was more interested in being able to IM a friend than in living longer.

Participation should continue as study designs and endpoints are developed. When enrolling for the study, patients can help recruit subgroups. Where communities distrust research, patients can help understand the issues and locate trusted voices in the community to build trust.⁶ Patient-Centered Core Impact Sets help understand the needs of patients with chronic disease, creating disease-specific lists of the effects patients identify as most important to them to guide research that aligns with patient-informed value elements. The concept is currently being developed and has potential to help researchers, patients, and others in the future.^{7,8}

During trials, patients should be involved in monitoring and adjusting study protocols. Patients can participate in safety surveillance, including data safety monitoring boards. At study completion, patients can take part in interpreting results and communicating with their communities. If people see why the trial matters, they will more likely volunteer for follow-up studies. Study patients can share their experiences and encourage others to follow the resulting treatment guidelines, improving outcomes.

The Patient-Centered Outcomes Research Institute (PCORI), an "independent, nonprofit research organization that seeks to empower patients and others with actionable information about their health and healthcare choices," funds comparative effectiveness research to help patients and other stakeholders make better informed decisions. Its creation was an important step in focusing public attention on the patient voice. "What do we know about my condition and how to treat it? How do alternative treatments compare? What can I expect from each option?"

PCORI created PCORnet[®], a national resource for patient-centered outcomes researchers. The organization is continually developing better ways to engage patients and amplify the effect of their voices.⁹ PCORI has published [Methodology Standards](#) to guide research that is meaningful to patients.¹⁰ Key points include:

- Measure outcomes that people representing the population of interest notice and care about (RQ-6)
- Engage people representing the population of interest and other relevant stakeholders in ways that are appropriate and necessary in a given research context (PC-1)
- Identify, select, recruit, and retain study participants representative of the spectrum of the population of interest and ensure that data are collected thoroughly and systematically from all study participants (PC-2)
- Use patient-reported outcomes when patients or people at risk of a condition are the best source of information for outcomes of interest (PC-3)
- Support dissemination and implementation of study results (PC-4). [Results should be publicly available in language understandable and actionable to as many people as possible in the population of interest.]
- Data-sampling plans should be designed to avoid selection bias (DR-1E)

Real-world evidence

Patient participation in large database studies (as research-team members, not observers) can improve the validity and usefulness of results.¹¹ Machine learning algorithms may be influenced by subtle biases in the training data or historical trends, or unconscious biases of the programmers, and can amplify these biases.¹² Patients can identify certain biases so that they can be corrected. Patients with lived experience anticipate barriers to applying results that researchers would miss, such as the impact of a time-consuming treatment protocol on a single parent navigating inflexible work and school schedules and meeting the logistic and emotional needs of patient and siblings. Patient input is required for economic models to reflect true value based on lived experience. The post-COVID remote work environment creates situations where model builders do not live in the environments their models represent. Consultation with patients can produce more realistic models.

Patients as full partners

In a patient-centric process, patients are partners. "I always

felt the medical staff was working *with* me, not *on* me, giving me the power of decision,” one patient with cancer explained. “They’ve advocated very strongly at times for certain things, but I was making the decisions. It’s the patient’s life. It’s their body.”¹³ For patients to be heard, they must speak researchers’ language, understand their thought processes, and know their constraints. Not all patients need extensive technical training, but each patient group should have informed advocates. To facilitate learning, the National Health Council, an umbrella organization for patient advocacy groups, offers a variety of online resources that provide technical knowledge for patients.¹⁴ The National Organization for Rare Disorders also provides education focused on the needs of their constituency.¹⁵

Patients in minority communities need education, too. Educators must go into those communities. The PATIENTS Program is “an interdisciplinary research team of community partners and researchers housed at the University of Maryland School of Pharmacy that works to change the way we think about research by creating a path for health equity.” The program reaches patients where they are, caring about them, and showing them that they can be involved as an important part of the process.¹⁶

Patient participation in large database studies (as research-team members, not observers) can improve the validity and usefulness of results.

Team members listen before they speak. “They actually care about what the patient wants. They actually ask the patients themselves, ‘What research would *you* like to see,’” says Gail Graham, Director of HIV Research at Mt. Lebanon Baptist Church in Baltimore. They help patients see “that they are the most important member of their treatment team. They’re part of the team working to save their life, to enhance their life, to prolong their life,” explains Cynthia Chauhan, a Patient Advisor. The PATIENTS Professors Academy offers a 5-week virtual training program for active participation.

The average advocate does not need more extensive technical training, but it is useful to have some “patient experts” who can converse at this level. The European Patients’ Academy on Therapeutic Innovation (EUPATI) trains experts “empowered to work effectively with the relevant authorities, healthcare professionals, and industry to influence the medicines development process for the benefit of patients.” Developed by patients with academic experts, the 1-year EUPATI Patient Expert Training Programme covers the lifecycle of pharmaceutical research and development and teaches patients how to contribute constructively at each stage. More than 250 EUPATI Fellows from Europe and elsewhere have completed this program. Over 70% hold leadership positions in a variety of patient organizations.¹⁷

Rare disease patient concerns

Rare disease patient advocates report that manufacturers listen to them more frequently than payers and health technology assessment (HTA) agencies.¹⁸ “Smaller biotechs seem to do better at this than Big Pharma, but there are still improvements to be made,” one advocate noted. “The focus for payers seems to be on what can get the job done the cheapest versus what’s best for the patient and caregiver. Decisions like this not only lead to wasteful spending, but the patient’s/caregiver’s needs still aren’t met.”

“You need to balance the needs of the patient for treatment with the need for experimentation.”

– Stanley Croke, MD, PhD

Patients with degenerative disease often appear normal at birth. It may take several months before parents notice missed developmental milestones. A diagnostic odyssey usually follows. One parent wished for “a durable treatment given soon after birth to ameliorate the disease or make it more manageable so patients could walk longer versus spending a lifetime in a power wheelchair, which has a domino effect on overall health.” Her challenges include “balancing work and family responsibilities as my son ages and needs 24/7 assistance, need for respite care, paying for costs not covered by insurance, finding accessible and affordable housing, marital stress, and unexpected hospitalizations.”

Her son’s condition affects the whole family. “Sometimes the devil is in the ugly details. My son has lost most of his upper body function. He can no longer scratch an itch, which may seem unimportant, but imagine what it means to a 16-year-old boy who has mosquito bites and has to call out for someone to come and scratch them for him? When his friends are playing sports, he has to be careful to stay out of the way of an errant ball because he can’t lift his arms up to protect his face from getting hit. These are the heartbreaking realities I witness every day—the little things that become so big. My son hasn’t slept a full night since he lost ambulation and can no longer turn himself over at night for comfort. We haven’t slept a full night since then either. Any treatment effect should be viewed within the context of caregiver experience. Value assessments can be somewhat useful but miss a lot if they’re not sensitive enough to actual lived experience. Caregiver experience/impact, such as sleep quality, physical pain as a result of caregiving, and mental health is rarely fully captured by these tools.”

Payers’ decisions often don’t make sense to her. “Wheelchair seat elevation or other functions like headlights are constantly denied as ‘not medically necessary.’ As a caregiver, this tells me they don’t think a person in a wheelchair needs to elevate chair height to enjoy dinner at a restaurant or be more independent by being able to reach differing heights; nor do they need

headlights to roll through a parking lot after dark so they don't get backed into by a car. It's so senseless and frustrating." Caregivers would like to have more assistive medical technologies to maintain independence, but question whether payers will cover them. Required access modifications to homes and vehicles often are not covered. Patients experience "battles with the education system, battles getting medical staff to recognize parent expertise, divorce leaving one parent to bear the majority of caregiving, and loneliness." Treatments that extend patient survival may leave aging parents worrying about who will care for the patient when they are unable.

The needs of atypical patients are often overlooked. According to Michelle Rice, a hemophilia advocate, the needs of her patient community are generally well understood and providers and payers are sympathetic, but "you can't reach every payer or every administrative agency so there are some who have never truly "engaged" directly with a patient advocacy organization or a patient."

"Consistently and systematically engaging patients across the lifecycle of medicine development creates value for patients, pharmaceutical companies, and society overall."

— Marc Boutin

"Hemophilia and related bleeding disorders affect all races, ethnicities, and genders," Rice explains. Because hemophilia is generally considered a male disease, "women tend to be underrepresented in clinical trials. Historically, women were categorized as 'symptomatic carriers' rather than 'hemophilia patients.' There has been a recent push to bring in more women and people of color in clinical trials." While there are more therapeutic options than for most rare diseases, Rice reminds us that "not all hemophilia patients bleed the same or respond the same to treatment." At the top of her wish list would be a treatment "that provides sustainable, consistent levels of hemostasis, prevents spontaneous bleeding, and resolves injury-related bleeding without needing to re-dose."

Patients with unique mutations are a special minority for whom targeted drug development is not commercially feasible. Stanley Crooke, MD, PhD, retired CEO of Ionis Pharmaceuticals, formed the nonprofit N-Lorem Foundation, which sequences the DNA of individual patients and synthesizes an antisense oligonucleotide to target the mutation. Crooke estimates a lifetime supply for one patient will cost around \$700,000 as the steady-state price he thinks they can achieve. Here too, researchers need patient input. "These are patient lives," he says, "so we try very hard to define the primary treatment goals that matter to the patient and secondary or exploratory goals and specific measures. You need to balance the needs of the patient for treatment with the need for experimentation."¹⁹

Manufacturers can support partnership

Manufacturers are finding different ways to engage patients. Marc Boutin, Global Head of Patient Engagement at Novartis Pharmaceuticals, is driving change at his company, "making medicines with patients, not *for* them."²⁰ For Boutin—an attorney, former patient advocate, person living with a chronic disease, and cancer survivor—it's personal. "Consistently and systematically engaging patients across the lifecycle of medicine development creates value for patients, pharmaceutical companies, and society overall."

"When we co-create patient-relevant endpoints with the patient community, we identify and validate fit-for-purpose measures, core outcome assessments, and the need for patient preference studies—all of which informs our regulatory submission," Boutin explains. "The resulting label defines our commercial strategy and informs our efforts to ensure that the right patients get access to life-altering medicines as quickly as possible." Patient engagement helps Novartis reduce costs by avoiding products that won't matter to patients, improving trial protocols, increasing enrollment, and reducing dropout rates. He believes this is "a true win/win...an investment in good decision making."

Boutin lays out a model for others to follow. "Together with patients and associates, we developed a vision, strategy, and framework for ensuring patient input into key decisions across Novartis. Rather than create a separate patient engagement process, we embedded our work in existing processes like the target product profile, integrated evidence, clinical development, and one-impact planning. As the patient voice permeates every aspect of the company, it reinforces our collective and personal purposes."

Medicine has traditionally been paternalistic. There is an asymmetry of scientific information that leads to unconscious bias that the professional knows what is best. When we listen to patients, we learn that there is an opposing asymmetry of information and understanding about their circumstances, desires, hopes, and dreams. Novartis has learned that "when you engage patients, you learn that how they feel, function, and survive are all important but weighted differently depending on their disease progression and personal goals. For example, some people living with schizophrenia do not want their treatments to stop their hallucinations—it's part of their creativity."

Novartis plans to implement "a new impact measurement framework designed to ensure systematic patient engagement, insight-driven decision making, and the generation of value for patients, healthcare systems, and Novartis." Other manufacturers are developing similar programs. Patients will come to expect this level of engagement and will need the resources to learn the technical skills they need to be full participants in a relationship where each side has knowledge that the other doesn't, each recognizes the value of what the other side knows, and they have a common language to communicate effectively with each other. Regulators are increasingly demanding patient experience data and HTA agencies are seeking evidence that demonstrates value to patients, Boutin observes.

Patient centrality and payers

Most payers have not had a patient-centric view, but as stewards of increasingly scarce healthcare dollars, they want to pay for what has the best value to patients. Payers listen to feedback from plan members, but they also need to hear from patient groups. However, most lack the resources in terms of expertise and budget to cover the costs. More awareness of the need and the emergence of virtual meeting technology is a game changer that allows patients and payers to communicate inexpensively.

HTA agencies connect patients and payers. It is more efficient for them to dialogue with patients and share the results with the payer community. In 2016, the Institute for Clinical and Economic Review (ICER) began to include a patient section in their reports. Patients' response to ICER's work has been mixed, and they are the first to point out ICER's shortcomings, but payers use ICER reports in formulary and coverage decisions. While few payers have time to read all the information ICER shares publicly, the reports' summary of patient concerns should begin to expand payer awareness.

Reading the ICER reports may encourage payer pharmacists to reach out to patient advocates directly. Sickle cell disease was reviewed by ICER in 2020.²¹ This condition affects 1 in every 500 African American live births, but until 2019, there were no new treatment options. ICER quoted frustrated patients who encountered unsympathetic emergency department staff that didn't believe them when they presented with acute pain in vaso-occlusive crises. Their stories caused Premera Blue Cross pharmacists to revise the opioid pain medication coverage policy to give patients with sickle cell disease the same exemption as cancer patients. Premera simply had no idea this problem existed. Once they learned about it, they found a simple way to help.²² Premera developed an ongoing relationship with the [Sick Cells](#) patient advocacy group and later arranged for a virtual presentation to the Premera Pharmacy and Therapeutics Committee.

Patient input has helped HTA organizations recognize that lack of patient diversity in clinical studies affects the representativeness of the results and decreases their value.

ICER again reviewed sickle cell disease in 2023, as 2 potentially curative gene therapies were pending US Food and Drug Administration approval, bringing new hope to patients with this devastating disease. Sick Cells continues to work with ICER and others "to improve value assessments for sickle cell disease through a transparent and collaborative approach, representation of patient and caregiver perspectives, high-quality databases that adequately account for the diversity of patients with sickle cell disease, and methods that support equity. Sick Cells works with patients, researchers, health

economists, payers, and providers to find the right approach to measuring cost and value for sickle cell disease."²³

Patient input has helped HTA organizations recognize that lack of patient diversity in clinical studies affects the representativeness of the results and decreases their value. ICER recommends that a threshold be established for "adequate representation of racial and ethnic populations in clinical trials." Deliberative processes should be used. HTA should promote a balance between population health and individual patient needs, so that limited resources are equitably distributed. Reviewers should note when clinical evidence does not adequately represent minorities.²⁴ ICER's topic selection criteria now include consideration of underlying inequities in the population of interest, favoring treatments that can potentially reduce those inequities. Early engagement with those communities is critical to success.

The [Innovation and Value Initiative](#) seeks to create "a US learning healthcare system supported by patient-centered health technology assessment and focused on high-quality, efficient, innovative, and equitable care for all people and communities."²⁵ Their work focuses on heterogeneity in patient populations.

Expanding possibilities with innovative technologies

Virtual meetings let researchers recruit a broader range of patients whose schedules don't permit travel to study sites. Patients can interact more frequently and participate more fully in the research. Low-income patients with logistic challenges are more likely to participate if travel is minimized. "We deal with families who are getting care at the closest center, even if it's not a specialty clinic, and have no way of taking time off work to commit to a trial. Some are struggling to keep their heads above water or have no accessible transportation," an advocate from the Little Hercules Foundation commented. Remote rural patients far from study centers may benefit from virtual technology if they have adequate Internet speed and bandwidth.

Creative means of remote data gathering can reduce participant burden and enhance interpretation of outcomes. For example, video capture data transmitted with a smartphone lets researchers view in-home performance of patients with muscular dystrophy, augmenting less-nuanced clinical trial endpoints with observations that reflect what matters to patients, the subtle variations in that caregivers see every day. This could provide supplemental evidence for regulators and guide appropriate treatment.²⁶ Regulators will need to change how they evaluate studies, validating new endpoints and reviewing new types of evidence. Payers must understand the methodology to evaluate such evidence when making formulary decisions.

Social media provides a way of gathering perspectives from informal conversations that patients might be reticent to share with investigators. Natural language processing will facilitate collecting and organizing this input. Machine learning algorithms can automatically detect adverse events in postings on public sites. This is particularly useful in pharmacovigilance because patients often don't report side effects.²⁷

Social media data can help researchers understand the subjective experience of a broader range of patients than beyond their trial population. Sentiment analysis assesses the ratio of positive and negative words in a post to infer the individual's opinion about a treatment. Comments regarding switching treatments are also useful. Of course, social media has well-known biases and "echo chamber" effects. People tend to present idealized versions of themselves, and those that eschew social media use entirely will not be represented. Nevertheless, social media may add valuable insights. Ethical considerations around data extracted from public postings need to be carefully examined.

Properly incorporated in research processes, patients can help us return to viewing populations as collections of diverse human beings for whom we strive to extend life and improve its quality. Their voices remind us that research subjects are people with lives, rather than problems to be fixed through "druggable" targets. As we include them in the design and execution of studies and interpretation of the results, they will help us identify population heterogeneities that impact treatment choices, helping us deliver improved outcomes and reduce numbers needed to treat, improving the cost-effectiveness of those treatments. ISPOR's mission is improving healthcare decisions. Patient voices can help us do that better.

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By the Numbers: Patient Centricity in HEOR

Section Editor: The ISPOR Student Network

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Defining Patient Engagement in Research



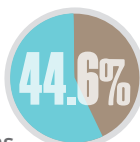
Patients and Caregivers as Key Stakeholders

PATIENT ENGAGEMENT

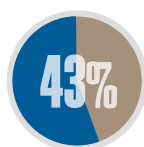
Less than 5% of eligible patients participate in clinical research.



44.6% of patients want more involvement than they currently have in their healthcare decisions in the United Kingdom.



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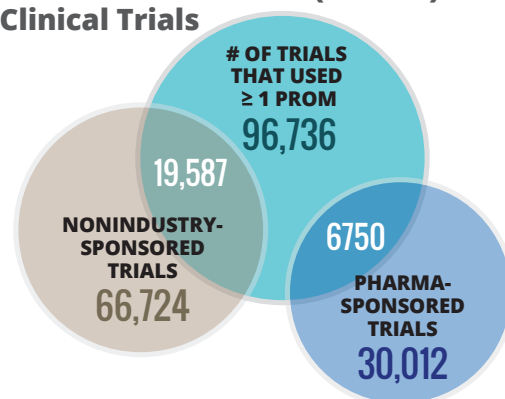


43% of the global population are caregivers for a family member or loved one.

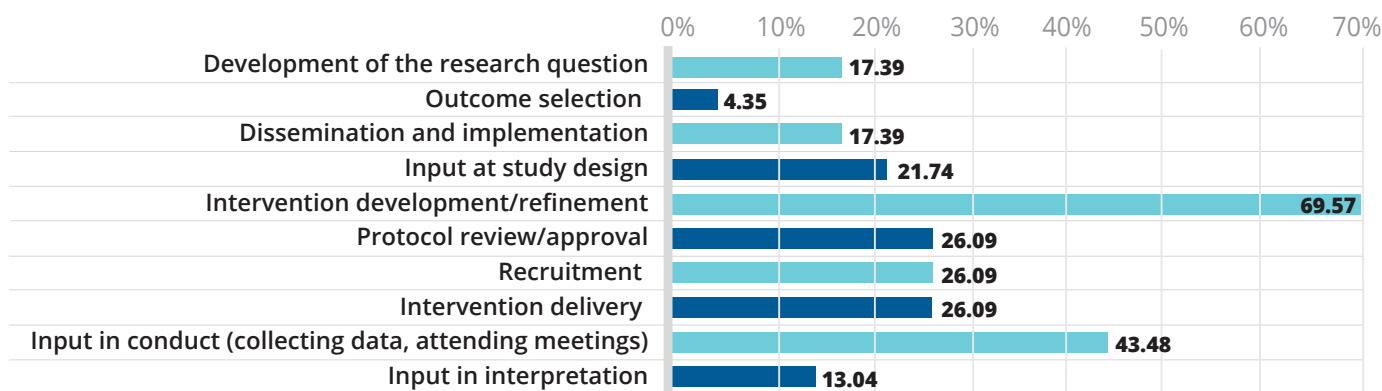
Informal caregivers provide an estimated \$600B worth of unpaid care to patients annually in the United States.

\$600B

Use of Patient-Reported Outcomes Measures (PROMs) in Clinical Trials



The prevalence of patient and caregiver engagement in published trials



Patient- and Caregiver-Perceived Challenges to Effective Participation in Health Technology Assessment Activities in Europe

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Patient engagement in health technology assessment strengthens the credibility of the decision-making process as treatments evolve and clinical outcomes become more complex.

Methodological challenges and a lack of concrete guidelines limit meaningful patient contributions to health technology assessment in Europe.

In addition to educating and training patient advocates and healthcare policy makers, it is the responsibility of health technology assessment (HTA) bodies to provide adequate opportunities and resources to optimize patient engagement throughout the HTA process.

Introduction

Encouraging patient engagement (PE) in the health technology assessment (HTA) process strengthens the equity, relevance, accountability, and credibility of decision making.¹ Patients and patient representatives are an important source of information, as their insights into the lived experience of disease improve our understanding of unmet needs and the impact of the disease/therapy in question. Many novel technologies lack tangible economic benefits but provide promising clinical outcomes.² These situations require that the lived experience of patients is captured to emphasize the potential benefit of emerging treatments and their potential value to those stakeholders most directly affected by their recommendation for approval—the patients.² Although the European Network for HTA (EUnetHTA) recognizes that patient perspectives are “an essential part of the evidence base that is integral to the interdisciplinary process of an HTA,”³ there is significant variability in PE among HTA bodies in Europe.⁴ As treatments

As treatments evolve and clinical outcomes become more complex, incorporating patient perspectives and experiences into the HTA process can aid in the development of more informed recommendations.

evolve and clinical outcomes become more complex, incorporating patient perspectives and experiences into the HTA process can aid in the development of more informed recommendations.² Our objective was to identify the challenges perceived by patients and their representatives for effective participation in HTA activities in Europe and to review the existing guidelines published by HTA organizations from the European Union (EU4) and the United Kingdom (UK) that address these challenges.

Our approach

We conducted a targeted literature review in PubMed to identify studies published between January 2012 and April 2022 describing the challenges reported by patients, caregivers, and patient representatives for active participation in HTA activities in Europe. Search terms included “patient engagement,” “health technology assessment,” “challenges,” “barriers,” “patient participation,” “patient involvement,” “stakeholder expectations,” “patient perspective,” “patient organization,” “patient representative,” “caregiver,” “carer,” “public involvement,” and “patient preferences.” Observational studies were included, whereas narrative and systematic reviews, non-English studies, and studies with participants from non-European countries were excluded. We also reviewed recently available guidance from the National Institute for Health and Care Excellence (NICE; UK), Haute Autorité de Santé (HAS; France), Institute for Quality and Efficiency in Health Care (IQWiG; Germany), Agenzia Italiana del Farmaco (AIFA; Italy), and Agencia Española de Medicamentos y Productos Sanitarios (AEMPS; Spain) that address these challenges to PE in HTA.

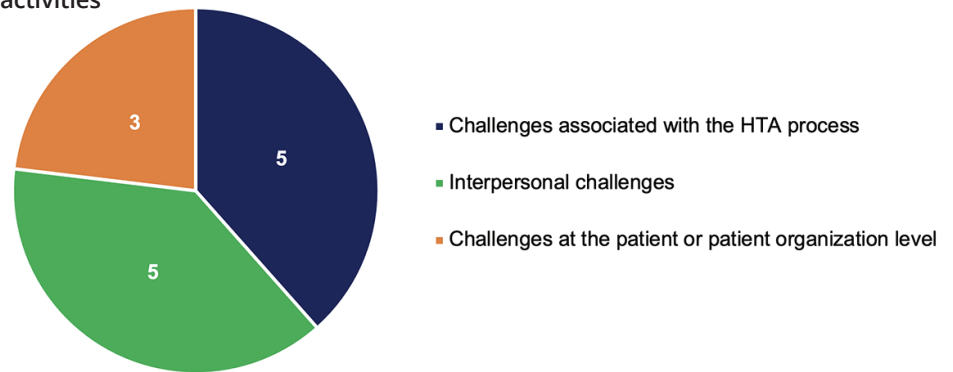
What do patients and patient representatives perceive as challenges?

The targeted literature review identified 12 cross-sectional studies involving patients, caregivers, and representatives from patient organizations across Europe.⁴⁻¹⁵ This included participants from the United Kingdom (n=5), The Netherlands (n=4), France (n=3), Germany (n=3), Italy (n=3), Ireland (n=2), Romania (n=2), Spain (n=2), Sweden (n=2), Switzerland (n=1), Belgium (n=1), Denmark (n=1), and Finland (n=1). Most of the studies involved patient organizations (n=10); patients and caregivers were involved in 3 studies, one of which also included patient organizations.⁴⁻¹⁵ The identified studies employed various methods including questionnaires (n=7), interviews (n=4), consultations (n=3), workshops (n=2), and seminar and focus group discussions (n=1),

as well as a combination of these to identify challenges to HTA involvement experienced by patients and patient representatives.⁴⁻¹⁵

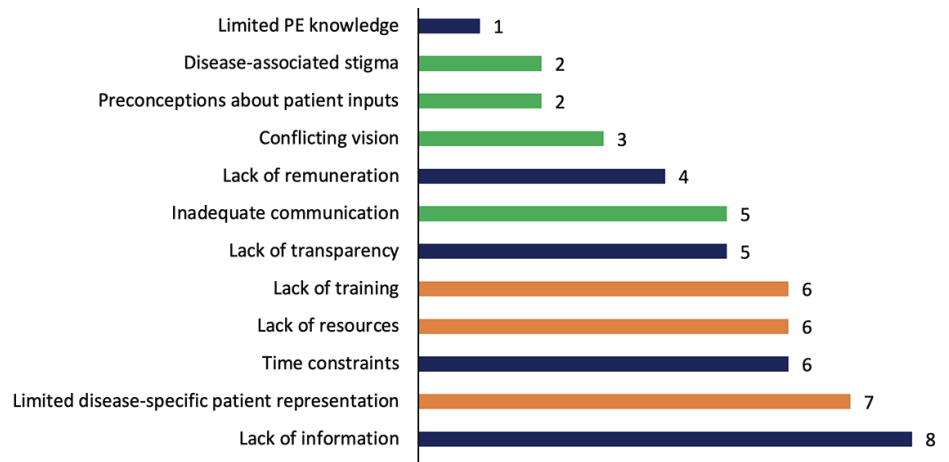
Across the 12 studies, 13 unique challenges were identified, including political, economic, sociocultural, methodological, and technological challenges.⁴⁻¹⁵ Most of the challenges experienced by patients and patient representatives were associated with the HTA process and the bilateral relationship between HTA agencies and the patients or patient organizations (Figure 1). Challenges for participation in HTA also occurred at the patient or patient representative level, such as limited disease-specific patient representation in patient organizations, (n=7), as well as lack of adequate training and resources for participation in HTA (n=6 each) (Figures 1 and 2).⁴⁻¹⁵ The lack of information from HTA agencies about the HTA process (eg, details about the technology being assessed and how reimbursement decisions are made) and HTA agencies overlooking the value of patient inputs (n=8, each) were the most commonly perceived barriers to effective PE in HTA (Figure 2).^{4,5,8-13,15} Specifically, in some cases, patient organizations perceived their involvement in the HTA process as “superficial” and “tokenistic.”^{15,10} Limited PE knowledge among HTA agencies was the least reported challenge (n=1).⁵

Figure 1: Studies reporting challenges for effective patient engagement in HTA activities



HTA indicates health technology assessment. Source ⁴⁻¹⁵

Figure 2: Challenges reported by patients and/or patient organizations for participation in HTA activities in Europe



HTA indicates health technology assessment; PE, patient engagement. Source ⁴⁻¹⁵

Do existing guidelines from HTA bodies address these challenges?

Of all the HTA bodies assessed in this search, NICE had the clearest guideline for how patients can and are expected to participate in the HTA process (Table 1).¹⁶ The NICE guideline specifies the patient expert nomination and selection process at the outset and details patient expert participation in committee meetings. Patients and patient representatives are involved early in the HTA process from the scoping stage in outlining the methods to the appraisal of technology assessment and scientific advice stage.¹⁶ The guideline distinctly outlines the role of patients and their representatives including their participation in workshops and committee meetings and provision of comments on recommendations.

Table 1: Guidelines addressing challenges for PE in the HTA process in Europe

Guidelines	NICE (2022)	IQWiG (2020)	AEMPS (2022)	AIFA (2022)	HAS (2022)
Patient or patient representative participation in committee meetings	✓	✓	✓	✓	✓
PE in the HTA assessment process	✓	✓	✓	None	None
PE in report review process	✓	✓	None	None	None
Encourage patient comments	✓	✓	None	None	✓
Recommend patient education	✓	None	None	None	None
HTA actions outlined for increasing PE	✓	None	✓	None	None

AEMPS indicates Agencia Española de Medicamentos y Productos Sanitarios; AIFA, Agenzia Italiana del Farmaco; HAS, Haute Autorité de Santé; HTA, health technology assessment; IQWiG, Institute for Quality and Efficiency in Health Care; NICE, National Institute for Health and Care Excellence; PE, patient engagement. Source ^{16,17,20,21,23}

NICE also recognizes that both strategy and support for including patients in the HTA process are necessary and provides proactive outreach, training, and mentoring by engaging a dedicated patient expert liaison and documenting the impact of the patient experts' contributions.¹⁶

IQWiG recognizes the importance of patients' and caregivers' perspectives by involving them in the selection of topics for HTA and integrating their perspectives in defining patient-relevant outcomes and scientific assessment.¹⁷ IQWiG welcomes stakeholder comments and considers these comments in its HTA. During dossier assessments and economic evaluations of technology, IQWiG invites comments from patients and patient organizations through formal questionnaire assessments. Patients and their representatives are also members of the Board of Trustees and have the opportunity to review the reports before user testing.¹⁷

The gaps in the existing guidelines reveal that the burden is on HTA bodies to ensure that patients and patient representatives are included and have access to the requisite resources for effective participation in the HTA process.

Patient participation in the HTA process in Spain is limited to representation in the Governing Council on technical committees such as the Committee for Medicines for Human Use and the Committee for Medical Devices.¹⁸ However, the Spanish Network of Agencies for Assessing Health Technologies (RedETS), which is responsible for the assessment of technologies for inclusion in the Spanish Common Benefit Portfolio, published a methodological guideline for patient involvement in HTA.¹⁹ The guideline encourages the contribution of patients or patient representatives in the protocol and preliminary report review process

and in the assessment for including patient-based evidence.¹⁹

In France, PE in HTA is still in the early stages and is limited to proposing topics for assessment to HAS.²⁰ Similarly, despite PE being in its infancy in Italy (ie, restricted to participation in Open AIFA meetings),²¹ AIFA is involved in enabling systemic and meaningful PE in HTA through its participation in the Patients Active in Research and Dialogues for an Improved Generation of Medicines project (PARADIGM), a European partnership aimed at enabling PE.²²

In 2018, the European Patients' Academy on Therapeutic Innovation (EUPATI) published specific recommendations for patient involvement in HTA. The guideline recommended that HTA bodies across Europe engage in outreach and educational activities, allow wider patient involvement, and provide compensation for patient involvement.¹ Although these recommendations were made 5 years ago, our study shows that methodological challenges still exist for patients and patient representatives, highlighting the need for improvement.¹¹ Although most of the guidelines identified in the present study were published after the 2018 EUPATI recommendations, the review of guidance documents showed that for the most part, PE in HTA is limited to proposing topics for assessment or commenting via questionnaires when PE could be much more robust, purposeful, and impactful.¹⁴ While NICE and IQWiG recognize the value of patient experts' involvement in the overall assessment process, including the patient's experiences with the disease and the given technology, adequate resources and information required for effective PE are minimal.^{4,16} Patients and their representatives often have to rely on publicly available data, clinical trial information, physicians, other patient organizations, existing HTA reports, conferences, media, or internet searches for information on the technology being assessed.⁴

Conclusions

Patients and patient representatives anticipate their involvement early in the HTA process with a focus on long-term sustained involvement throughout

all phases of the HTA process as opposed to discrete engagement events.^{6,7,10-12} Specifically, patients and patient representatives prefer to be involved in all HTA phases such as defining objectives and problems; identifying and prioritizing technologies for evaluation; assessing ethical, social, and economic issues; and developing a patient-friendly version of the results for public consultation, dissemination, and documentation.¹¹ The gaps in the existing guidelines reveal that the burden is on HTA bodies to ensure that patients and patient representatives are included and have access to the requisite resources for effective participation in the HTA process. Considering the time and resource constraints experienced by patients and their representatives, there is a need for HTA agencies to provide adequate training, establish effective communication channels, and increase transparency to enhance and facilitate effective PE in the HTA process.^{4,8,9,11} It is imperative that HTA bodies in Europe work together with patients and patient organizations to address these challenges and create a shared vision for enhanced PE throughout the HTA process.

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Leveraging ePRO Paradata for Patient-Centered Trial Designs

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Patient-reported outcome (PRO) measures paradata (ie, data about the data generation process) are a readily available data source collected by any electronic PRO device that can provide a lot of valuable insights about how different patients interact with PROs.

Younger patients have lower adherence and spend less time completing PROs than older patients. Patients who had a higher adherence rate before randomization were also more adherent throughout the trial.

These insights show that including adherence as an inclusion criterion can help prepare patients to use the ePRO device every day during the run-in period and improve their compliance after randomization.

Introduction

Patient-reported outcome (PRO) instruments play a vital role in the drug development process by gathering valuable data directly from patients, capturing their perspectives on symptoms, functioning, and overall health-related quality of life.¹ Typically, these data are collected through validated self-reported questionnaires. Nowadays, electronic PROs (ePROs) have become a standard, utilizing devices like tablets or smartphones.² This is driven by growing evidence that ePROs offer benefits such as improved adherence,³ reliability, and reduced secondary data entry errors⁴ compared to traditional pen-and-paper methods.

Patients who demonstrated higher adherence prior to randomization maintained higher adherence levels to the end of the trial.

However, ePRO devices offer more than just the ability to collect patient responses. They also gather additional data known as paradata, which include information about the data collection process itself. Paradata can include details such as timestamps indicating when patients started and finished the questionnaire, login attempts, and device power levels. Although the exploration of such datasets in health economics and outcomes research literature has been limited, recent work has highlighted their potential value.⁵ Analyzing paradata can offer insights into patients' interactions with ePRO devices and PROs, leading to improvements in patient-centric clinical study designs and a better measure for the amount of effort that patients must dedicate to complete PROs. Without requiring additional work from the patient themselves, these patient-centric analyses can contribute to our understanding of the respondent burden in clinical trials.⁶

Methods

We analyzed data from the OSTRO

study (NCT034012297), a phase III, interventional, randomized, placebo-controlled, double-blind, multicenter, longitudinal, respiratory clinical trial conducted between 2017 and 2020 investigating benralizumab in patients with nasal polyposis.

The study included a PRO measure, the Nasal Polyposis Symptom Diary (NPSD),⁸ which was completed every morning for up to 80 weeks (including the 56-week-long treatment period) on an electronic device that captured the start and end time of each completed assessment. The 360 patients included in this analysis have completed over 162 thousand daily NPSDs and spent almost 100 person-days of collective effort.

To identify factors driving patient adherence and response time (ie, the time that it took a patient to complete the daily NPSD), we used general linear mixed-effects models to account for the correlated nature of the data coming from the same patient, site, and country.

Findings

Prerandomization adherence is a strong indication of subsequent adherence

In the OSTRO study, the NPSD supported coprimary and multiple secondary endpoints, which were all analyzed as changes from baseline variables. Before enrolling in the study, patients had to meet a minimum adherence requirement for the NPSD during the 14 days leading up to the randomization visit in order to generate sufficient baseline data. Patients were aware of this expectation and agreed to be adherent by signing informed consent forms. This criterion did not introduce any statistically significant bias in the baseline characteristics of the population other than adherence.

We aimed to determine if the level of adherence to the NPSD before randomization could predict patient adherence throughout the trial. Patients who completed the NPSD every day in the 2 weeks preceding randomization were considerably more likely to maintain higher adherence throughout the

trial. This finding was supported by a multivariable model that adjusted for patient characteristics (such as age, ethnicity, sex), research site, and country, resulting in an odds ratio of 2.43 (99.9% CI: 2.31-2.62). To illustrate this finding, **Figure 1** shows the average adherence levels throughout the trial for different patient groups categorized by their pre-randomization adherence. The cohorts were divided into 3 groups: (1) those who completed the NPSD for all 14 days, (2) those who completed 13, and (3) those who completed fewer than 13. Although adherence decreased over time for all groups, patients who demonstrated higher adherence prior to randomization maintained, on average, higher adherence levels to the end of the trial.

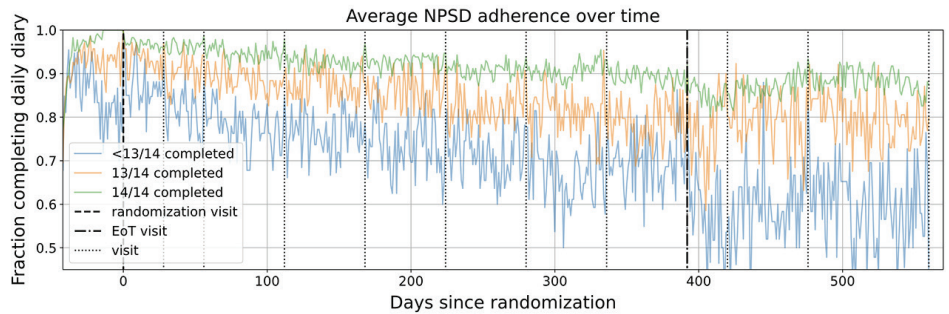
This finding supports using prerandomization adherence as an eligibility criterion for trial enrollment to ensure a high level of PRO completion rates, which is especially important when that PRO supports key endpoints in the study.

Patient completion time decreases with experience and increases with age

The paradata collected from ePRO devices offer valuable insights into the effort patients invest in completing PROs. By analyzing the start and end timestamps of the NPSD, we discovered that both patient age and previous experience with the tool had a notable impact on completion time. **Figure 2** demonstrates these findings, indicating that response time decreased rapidly for all age groups (divided into equally sized quantiles by age) across the first 30 days of NPSD completion. The level of decrease continued but at a more moderate rate throughout the remainder of the trial. Our analysis also revealed that older patients took significantly longer to complete the PRO, with the patients in the older cohort taking twice as long than the patients in the younger cohort.

The paradata alone cannot explain why we see such patterns. Older patients may find dealing with ePRO devices more challenging, which would explain why they take more time completing the PROs, but our findings are also in line with previous research that shows that older people may read at a slower

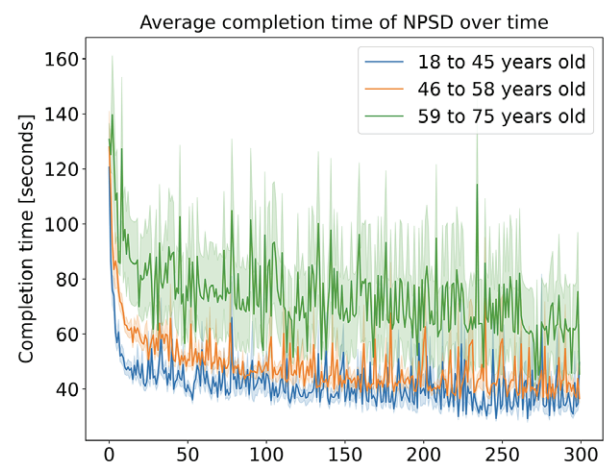
Figure 1: Average NPSD adherence over time of all the patients (325 patients) who completed the OSTRO study divided into 3 equally-sized groups by their pre-randomization adherence (ie, how many times the patient completed the NPSD in the 2 weeks prior to randomization visit). All patients are time indexed to the randomization visit. The dotted lines show planned visits according to the protocol but the actual visit date for each patient may vary up to +/- 7 days post-randomization



NPSD indicates Nasal Polyposis Symptom Diary

Figure 2: Average completion time (and standard error of the mean shown as a shaded area) of NPSD for OSTRO patients divided into 3 equally-sized groups by age.

NPSD indicates Nasal Polyposis Symptom Diary



rate.⁹ The quick decrease in response time from the beginning of the study until the end (which is especially rapid in the first month) may be explained by independent educational research findings on repeat reading that showed the exposure to the same text on multiple occasions not only increased the reading speed but also improved reader comprehension.¹⁰ Further research will be required to find the comprehensive explanation of these trends.

Alerts and reminders drive ePRO response behavior

We can also use the PRO start timestamps to analyze how PRO completions are distributed over the daily response window. **Figure 3** displays the start times for NPSD in the OSTRO trial during the 6-hour morning window.

The prominent spikes at 9:00 AM, 9:25 AM, and 9:50 AM correspond to the initial default reminder setting on the device and the two 25-minute snooze options, respectively. Patients also had the freedom to modify the default reminder time, which might explain the presence of other spikes.

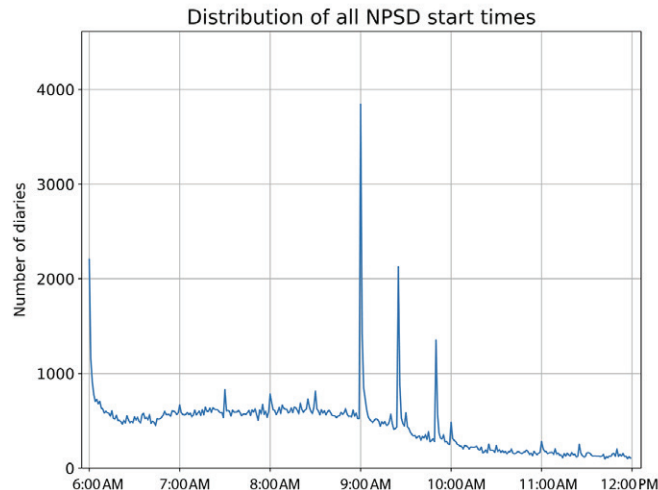
Data collected from a large cohort of diverse patients like these could guide clinical study teams to design better alert and reminder systems tailored to specific populations.

Conclusions and Outlook

Analyzing adherence and timestamps paradata from ePRO devices in large longitudinal clinical trials offers valuable insights into patient behavior that would be challenging to obtain otherwise.

Figure 3: Number of NPSDs that were started in every minute of the morning window across the entire OSTRO trial (only treatment period included). The 9:00 AM spike shows potential reminder alert effects followed by the default 25-minute snooze button effects.

NPSD indicates Nasal Polyposis Symptom Diary



These devices have the potential to provide a wealth of additional raw data that can be explored for further behavioral insights.

While some patient populations may face more challenges using ePRO devices compared to pen-and-paper, with ePRO we can continuously monitor signs of problematic patient-device interactions such as failed login attempts, devices running out of power, or PROs timing out. If we notice an unusually high number of such events with a specific device or at a particular site, it could suggest that a patient is struggling with technological challenges or that the site requires additional training and resources, respectively. By retrospectively analyzing these data from multiple studies, we can identify trends at a population level and improve future ePRO device setup to anticipate and prepare for such issues before a clinical trial begins. One of the main challenges is that ePRO device providers rarely collect and share this kind of paradata with sponsors by default. To facilitate this work in the future, clinical trial sponsors should require more comprehensive

data collection and sharing agreements in their trials.

Furthermore, we could leverage ePRO paradata to design better PROs. If the device records the time taken by patients to complete each PRO and tracks their journey through the PRO (including detailed logs of their answers), it can offer a convenient way to identify cognitively challenging questions. While these types of data may not be currently collected by default, there are no technical obstacles preventing it from doing so. Such analyses would empower clinical trial sponsors, ePRO device providers, and PRO developers with actionable patient behavior insights that can be used to enhance the patient experience without requiring any additional effort from the patients themselves.

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Good Publication Practice: Values for Health Economics and Outcomes Research Professionals

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Recognizing the value of HEOR experts to publications planning and management, the Good Publication Practice Guidelines for Company-Sponsored Biomedical Research: 2022 Update (GPP 2022) has an expanded scope to accommodate the work of ISPOR stakeholders.

Specialists in HEOR now have a clear pathway to organize publications activities.

Attention to the expertise of HEOR professionals in the context of publications will improve general understanding of clinical research and practice.

Introduction: The Importance of HEOR and RWE

Health economics and outcomes research (HEOR) and real-world evidence (RWE) provide valuable insights into both economic and health outcomes for healthcare interventions, considering cost-benefit and budget implications. These data provide clinicians with an enhanced understanding of effectiveness, safety signals across diverse patient groups, and possible impacts on a population basis for various demographic groups. Such findings are also used for health technology assessments (HTAs), formulary decisions, regulators, and funding bodies. Thus, HEOR and RWE experts routinely publish research results and may encourage the registration of RWE studies in the [ISPOR RWE registry](#).

ISPOR has shown a commitment to the continual improvement of publications and communicating research findings where they are needed. Groups such as [ISPOR RWE Task Forces](#) do important work to bring these findings to those who need them, including patients and other nontechnical decision makers. Individual experts also play important roles in publications. Like subject matter experts in any biomedical field, HEOR and RWE professionals may serve as

authors, advise colleagues on research design or publications, and review such work within research teams or as peer reviewers (**Table 1**). For research about marketed or investigational medicinal products or other collaborations with industry sponsors, additional logistical and ethical considerations may affect this work.^{1,2} For these reasons, the Good Publication Practice (GPP) Guidelines for Company-Sponsored Biomedical Research: 2022 Update¹ was designed to apply across scientific areas and is now more compatible with HEOR and RWE publications as a general rule. Assisting a wide range of healthcare stakeholders, GPP 2022's acknowledgement of HEOR and RWE as integral to biomedicine supports value-based decision making across all levels of formulary approval and resource utilization and helps promote the ongoing work of ISPOR members in improving publication quality.

We provide a high-level overview of GPP and its application for HEOR and RWE audiences with an emphasis on the increasing involvement of patients, caregivers, and patient advocates in research publications.³ Efforts to expand the reach of research findings also include a rise in the publication of plain language summaries (PLS), often as a

Table 1: Possible Roles for Subject-Matter Experts Related to Publications of Company-Sponsored Research

Role	Function
Author	Meets relevant criteria to be listed as an author on a publication, such as making contributions to study design or conduct, analyzing data, and providing critical review of the manuscript
Investigator	A member of a study group or team who contributes to research conduct and oversight
Lead Author	An author who provides guidance and leadership over a publication—this role often falls to the person who provided similar leadership for study design and conduct
Reviewer	Provides critical feedback on a publication draft but does not contribute to the manuscript or meet other authorship criteria
Steering Committee Member	Serves as part of an advisory group to help guide author teams and researchers toward appropriate publication settings (eg, journals and professional conferences), publication plans, and day-to-day practices. Experts in subspecialties may be called on to advise experts in related or more general fields of study

“short synopsis of a piece of research presented in a way that is accessible to a broad readership, including nonspecialist healthcare professionals and lay audiences, including patients.”⁴ HEOR and RWE experts are important collaborators who have an important part to play in enhancing and forwarding these publication practices.

Good Publication Practice *The Need to Expand*

GPP was originally designed to parallel good clinical practice and consequently focused on publications of clinical trials, especially randomized controlled trials.^{1,2} Through the influence of the International Society of Medical Publications Professionals (ISMPP), GPP became incorporated into an ever-increasing number of publication policies at sponsoring companies and medical communications agencies.

Over time, however, it became evident that attention to additional scientific areas was needed, given the extent to which subject-matter experts from outside clinical research engaged with publications. One specific strategy for updating GPP 2022 was to acknowledge

that biomedical research extends beyond the clinical trial and that HEOR and RWE are important scientific areas that required more explicit inclusion. By removing many specific references to clinical publications and mentioning HEOR and RWE wherever applicable, GPP 2022 pulled these areas into the mainstream. Integrating all stakeholders into GPP 2022 was intended to help prevent situations in which HEOR and RWE become a special case or an afterthought.

GPP 2022’s acknowledgement of HEOR and RWE as integral to biomedicine supports value-based decision making across all levels of formulary approval and resource utilization.

However, it is noteworthy that the general activities associated with scientific specialties like HEOR (**Table 1**) also apply to patients, caregivers, and patient advocates, who “should be regarded as experts who may give

important input into publications.”² While GPP emphasizes the value of many diverse stakeholders and acknowledges HEOR and RWE as an integral part of the publication landscape, it also recommends that patients, caregivers, and patient advocates be included in publications whenever possible, particularly for programs associated with rare or chronic conditions.

Overview and New Developments

GPP 2022² presents ethical and practical planning principles for biomedical publications in the main text; a detailed supplement presents further information and guidance about day-to-day practices, all of which may apply to HEOR and RWE colleagues and research. **Table 2** provides a list of some key considerations for HEOR and RWE professionals and where to find them in GPP 2022.

New developments in GPP 2022 reflect increasing efforts in the past few years to make the outputs of scientific and medical research accessible to a broader audience than its traditional readership. This practice has obvious applications for RWE and HEOR research, as reflected in

Table 2: Good Publication Practice Contents of Interest to HEOR Professionals²

Location	Section	Summary of information relevant for HEOR and RWE
Main Manuscript	Ethical Principles	<ul style="list-style-type: none"> • Adhere to relevant research and publication-related ethical principles • Provide appropriate disclosures and data while protecting patient privacy • Avoid commercial interests in publications • Promptly address any problems that may occur • Support accessibility, communication to lay audiences, and patient inclusion in publications • Consider marginalized groups, and regional and cultural differences • Follow appropriate guidelines evenly for all contributors • Detail roles and responsibilities in writing
	Practical Planning	<ul style="list-style-type: none"> • Plan publications in advance of data availability • Develop operating procedures to ensure good practice • Keep auditable records
Supplement	Steering Committees	<ul style="list-style-type: none"> • Identify roles and responsibilities in writing • Include relevant participants • Convene before data are available • Identify end dates
	Publication Plans	<ul style="list-style-type: none"> • Include all relevant studies and information • Ensure that problems such as duplicate publication are avoided • Consider preprints for appropriate scientific areas—avoid for clinical trials except in case of medical need
	Publication Working Groups	<ul style="list-style-type: none"> • Detail membership, communication steps, and ending
	Authorship and Contributorship	<ul style="list-style-type: none"> • Ensure that all relevant contributors are acknowledged • Follow appropriate criteria for authorship • Review author lists again during peer review • Develop author agreements
	Publication Process	<ul style="list-style-type: none"> • Outlines process for an individual publication
	Documentation	<ul style="list-style-type: none"> • Lists minimum records to keep

part by the work of the [ISPOR-ISPE-Duke Margolis RWE Transparency Initiative](#), as well as for increased involvement from patients, caregivers, and patient advocates. GPP 2022² is the first such guidance to present information on PLS and other enhanced content—which might include infographics or videos—that is published as part of the publication.

New developments in GPP 2022 reflect increasing efforts in the past few years to make the outputs of scientific and medical research accessible to a broader audience than its traditional readership.

GPP 2022 recommends developing a PLS for all types of research. For example, text-based PLS are recommended to be submitted with any clinical trial publications following the CONSORT guidance and for “any other publication of clinically relevant information about any currently marketed product.”² Standalone PLS are another option that may be relevant for HEOR and RWE studies.² Further contributions are needed from groups such as ISPOR to refine general practice regarding PLS, develop practical models, and continue their efforts in the ongoing improvement of the biomedical publication landscape.

Experts in HEOR and RWE are at the vanguard of several initiatives in company-sponsored research, such as increasing transparency and the involvement of patients in the publication process.

The benefits of patient engagement in developing medicinal products from the preclinical phase onward have been discussed in numerous publications, and efforts to define best practices are ongoing.^{5,6} While early attention focused on clinical trials, the value that patient engagement brings to HEOR and RWE is also now being recognized, for example with funding body PCORI’s Public and Patient Engagement program.⁷ While patients and their caregivers are a clear

audience to benefit from PLS, where they can help support patient involvement HTA and HEOR,⁸ there are numerous other audiences to whom they provide value, including regulatory bodies and payers.⁹

GPP: Opportunities for HEOR and RWE Leadership

Aside from the obvious need for experts to author their own research, HEOR and RWE experts should be involved across additional publications activities, as appropriate to the research stage of a program or product. For instance, steering committees advise teams on how and where to publish research and whether enhanced content may be useful for specific datasets.² Although a steering committee may be helpful for larger projects within a specific HEOR and RWE remit, a specialized HEOR/RWE steering committee may provide advice across clinical programs.² Another option is for individual HEOR and RWE experts to serve within various steering committees for applicable clinical development programs. Steering committee membership generally brings with it the responsibility for contributing to and reviewing publication plans or specific publications.² As with steering committees, publication plans might exist to cover the HEOR and RWE remit, or individual applicable HEOR and RWE publications might be included within overarching plans for specific products or programs.²

The inclusion of both HEOR and RWE publications within the GPP framework illustrates the maturing field of value communications and the expanding role of healthcare decision makers.

Another consideration relevant to HEOR and RWE colleagues is in the attribution of authorship. GPP 2022 recommends that all criteria for contributors and authors should be applied evenly to all colleagues, as consistent with journal and conference guidelines. Author agreements are recommended and

might be applicable to HEOR and RWE experts as well as clinical investigators.²

Best practices for working with medical writers are also reflected in GPP 2022.² Given that HEOR and RWE experts may serve as the lead writers for their publications, processes used by professional writers may provide a helpful context or labor-saving information. As HEOR and RWE experts are included in more publication’s teams, they may be called on to work with professional writers.

For many topics, GPP 2022 provides a high-level overview as well as helpful references that can be used to inform practice on individual teams.

Conclusions

The GPP 2022 expanded in important ways by recognizing the need to include HEOR and RWE peer-review publications. This new inclusion provides significant recognition of the value these publications offer to scientific literature and coincides with the US Food and Drug Administration’s ongoing expansion of the acceptance of HEOR and RWE data for their evaluation and approvals of drugs and devices.

GPP 2022 recognizes the importance of RWE publications, which draw insights from real-world data, reflecting efficacy results and side-effect signals from interventions in medical practice. The inclusion of both HEOR and RWE publications within the GPP framework illustrates the maturing field of value communications and the expanding role of healthcare decision makers.² Published evidence-based data, both economic and clinical, guide resource utilization for healthcare authorities, both private and at the federal, state, and local government levels. The recent pandemic shed light on the importance of real-world data to improve delivery and mitigate significant discrepancies within our nation’s healthcare sector. That the GPP 2022 update openly acknowledged HEOR and RWE publications is a testament to our evolving need for a wider set of evidence and economic analysis tools in medical research and practice management to support best practices in public health and resource utilization.

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An Invisible Burden: The Underrecognized Costs of Posttraumatic Stress Disorder Among Family/Friend Caregivers

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There is a growing awareness of the essential role of family and informal caregivers and the physical, mental, and economic strain they experience.

The prevalence of posttraumatic stress disorder among caregivers is generally found to be from 12% to 30%, which is similar to what is seen among military veterans.

We estimate the excess direct healthcare costs of posttraumatic stress disorder in informal caregivers to be >\$74 billion annually in the United States.

Introduction

According to the American Association for Retired Persons and the National Alliance for Caregiving, more than 1 in 5 Americans provided informal, unpaid caregiving services in 2020, caring in a nonprofessional capacity for an adult or child experiencing illness or disability.¹ Often referred to as family/friend caregivers, the burden experienced by such individuals is well established, particularly as informal caregiving becomes more common due to an aging population, and in light of the COVID-19 pandemic, which not only increased the need for informal caregiving but also added to the weight carried by existing caregivers as many healthcare services became home-based.²⁻⁴ Across the age spectrum and around the world, unpaid caregivers provide necessary services to a family member, friend, or other individual with whom they are connected, helping them to potentially delay or avoid the need for admission to a long-term care facility.¹ This scenario, while benefitting

More than 1 in 5 Americans provided informal, unpaid caregiving services in 2020, caring in a nonprofessional capacity for an adult or child experiencing illness or disability.

some caregivers by providing them with a sense of purpose and meaning, often results in disruptions to caregiver quality of life (QoL) and produces a considerable societal burden due to decreased productivity and disruptions to work.^{1,5-8} More specifically, family/friend caregivers experience impaired QoL, increased physical morbidity, lower health utility scores, higher rates of absenteeism and presenteeism, greater overall work impairment, and employment loss associated with the strain of caregiving.⁵⁻⁸ In addition, the caregiver population is

reported to have impaired mental health and a high prevalence of psychiatric disorders, particularly clinical depression and anxiety disorders.⁷⁻⁹

One area of notable relevance to the caregiving population is trauma and stressor-related disorders, including posttraumatic stress disorder (PTSD). Based on the current diagnostic criteria for PTSD,¹⁰ caregivers are a population at risk. The event-related criterion for a PTSD diagnosis is *Exposure to actual or threatened death, serious injury, or sexual violence*. The first 2 experience qualifications for this criterion are (1) *Directly experiencing the traumatic event(s)* and (2) *Witnessing, in person, the event(s) as it occurred to others*.^{10,11} Traumatic event(s) relevant to the family/friend caregiver population may include their care recipient being diagnosed with a life-threatening illness, undergoing a life-threatening medical procedure, or being admitted to a hospital or intensive care unit (ICU), among other events.¹²⁻¹⁴ Moreover, caregivers may often witness serious injury or threatened death of their care recipient in situations such as dementia or mental illness and may themselves be the target of psychological abuse or serious physical threats in some cases.^{15,16}

While several studies have explored the prevalence of PTSD in caregivers, it is likely to be underreported due to a number of interrelated factors, including difficulty distinguishing it from other disorders and/or more general emotional distress, a trend of PTSD under- and misdiagnosis in general, and diagnostic challenges relating to the nature of caregiving, where the focus of the caregiver and the healthcare team is primarily on the care recipient.¹⁷⁻²⁰

PTSD has one of the highest economic burdens among mental disorders, as illustrated by a recent economic evaluation showing a per person excess cost of PTSD higher than what has been reported previously for anxiety, attention-deficit hyperactivity disorder (ADHD), or

major depressive disorder.²¹ Comprising direct healthcare costs, direct nonhealthcare costs (eg, substance use disorder, disability), and indirect/societal costs (eg, unemployment, reduced productivity at work), the total costs related to PTSD were \$232 billion in the 2018 US population, higher than those reported in other studies for anxiety, ADHD, bipolar disorder, or schizophrenia.²¹ To our knowledge, there have been no studies exploring the economic burden of PTSD specifically in the family/friend caregiver population. The ongoing research described below aims to better characterize this

Family/friend caregivers experience impaired quality of life, increased physical morbidity, lower health utility scores, higher rates of absenteeism and presenteeism, greater overall work impairment, and employment loss associated with the strain of caregiving.

burden in order to facilitate further study on the economic and societal consequences of caregiver PTSD.²² Understanding this burden could help to inform education and awareness initiatives for healthcare providers and caregivers, and support the continued implementation of screening programs for early intervention, all of which have been recognized and recommended for at-risk caregiver populations but remain underutilized.^{4,18,20,23} Psychological therapies are the standard-of-care in PTSD, although pharmacotherapy may be used in some cases.¹¹

Prevalence of PTSD in Family/Friend Caregivers

Our first step in assessing the economic burden associated with PTSD in caregivers was to estimate the prevalence rate. Using PubMed searches and a citation-mining approach, we conducted a targeted literature review of existing research on the prevalence of PTSD in family/friend caregivers globally

as well as the costs associated with PTSD in civilian (nonmilitary) populations in the United States. Prioritizing the most recent studies (published since 2010), we identified 32 publications relevant to these topics—30 on the prevalence of PTSD in the target group of family/friend caregivers, and 2 reporting on the economic burden of PTSD in civilian populations. Our search for PTSD prevalence estimates was not limited to US studies in order to gather a large, diverse dataset. While the prevalence of PTSD is largely consistent across US and ex-US studies, further analysis would be needed to confirm that global PTSD prevalence estimates in family/friend caregiver populations are applicable to a US economic analysis.

In our review of the prevalence studies (**Table**), PTSD rates among family/friend caregivers were remarkably similar to those reported for military combat veterans. The 30 studies we identified included caregivers of patients within a variety of clinical situations, including severe mental illness, severe and/or chronic medical issues in both children and adults (including ICU and neonatal ICU admissions), dementia, and cancer. PTSD prevalence rates ranged from 3% to 82.9%, varying with patient age, patient diagnosis/clinical situation, and criteria used to define PTSD, among other factors. More than half of the 30 studies reported prevalence rates between 12% and 30% (**Table**), which closely mirrors the 11% to 30% range reported by the US Department of Veterans Affairs for PTSD among combat veterans.²⁴ Of note, one study found no significant difference in the prevalence of PTSD between a population of familial caregivers and other at-risk groups such as emergency first responders, military veterans, and nurses.¹⁶ Although the identified studies utilized a variety of measures for the assessment of PTSD and its severity, the majority require moderate to severe symptoms in order to establish the presence of PTSD (**Table**).

Economic Burden of PTSD in Non-Military Populations

To derive costs most closely in line with our target population, we limited the economic burden aspect of our search to nonmilitary populations in the United States. While literature

describing costs in this population is limited, the most recent publication we identified reported an annual excess direct healthcare cost per patient of \$13,016 for pooled Medicare, Medicaid, commercially insured, and uninsured groups in 2018 (adjusted to \$13,933.47 in 2020 USD), using PTSD prevalence estimates in the US population.²¹ While the main drivers of direct healthcare costs in this study were not reported, direct healthcare costs included both medical and pharmacy components.²¹ The other identified study reported mean per patient annual direct costs of \$18,753 and \$10,960 for Medicaid (n=9114) and privately insured (n=9720) populations, respectively (2008 USD; adjusted to \$26,726.51 and \$15,620.04 in 2020 USD, respectively).²⁵ The main cost drivers in Medicaid and privately insured patients were outpatient or other services (45.8% and 49.8%, respectively) and inpatient services (22.9% and 24.3%, respectively).²⁵ In the absence of economic data specific to the family/friend caregiver population, we recognize that a key part of this research must be the contextualization of the caregiver population in the greater body of literature on economic outcomes in civilian PTSD.

Estimating the Economic Burden of PTSD in the Target Population

Using a simplistic model without severity/symptom matching, we calculated an annual excess direct healthcare cost of PTSD in the caregiving population of more than \$74 billion USD for 2020 (**Figure**). In comparison, the estimated annual excess direct healthcare cost attributed to PTSD in 2018 in the US military population was ~\$10 billion, or ~\$10.7 billion in 2020 USD.²¹ While the present analysis focused solely on direct healthcare costs, the overall excess costs related to PTSD in the caregiving population are likely to be even greater if indirect costs such as lost productivity and unemployment are included. Incorporating indirect costs would require further analysis of the age distribution and demographic variables of family/friend caregivers.

The initial model presented here is based on several assumptions that remain to be refined. The populations and methodologies in the studies used to estimate PTSD prevalence were

Table. Studies reporting PTSD prevalence in family/friend caregivers^a

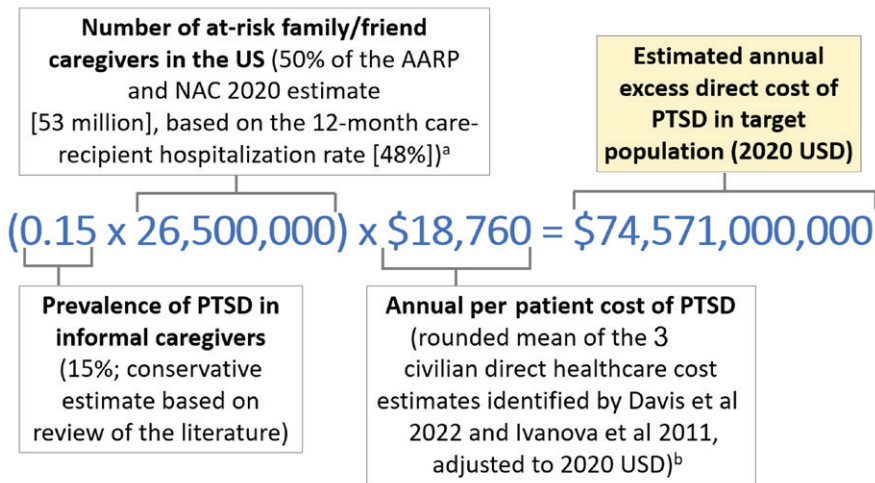
Source (Country/Region)	Study Design	Clinical Situation of the Care Recipient	Caregiver population (N)	PTSD Assessment(s) Used	Prevalence Rate
Systematic Literature Reviews					
Benyo et al, 2022 (NR) ³⁴	SLR	Patients with head and neck cancer (age not specified)	Various (N=1745) 77% partners/spouses	PSS-SR, PCL-C	13% to 29%
Corsi et al, 2021 (NR) ³⁵	SLR	Children with severe physical illness	Parents of patient (N=409)	NR	0% to 28%
Carmassi et al, 2020 (Multinational) ³⁶	SLR	Children, adolescents, and young adults with life-threatening or disabling diseases	Various (NR)	Various; IES-R most common	4.44% to 82.9%
Carmassi et al, 2020 (NR) ³⁷	SLR	Adult patients with severe physical illnesses	Various (NR)	IES, IES-R, PTSS-10, PC-PTSD, CIDI, PSS-SR, HTQ, PDS, PCL-C, PCL-S, PCL-5, PDS-5, PTCL, Modified PTSD Symptom Scale, SCID-5	11% to 74.1% ^b
Studies in Caregivers of Adult Patients					
Mashinchi et al, 2022 (USA) ¹⁶	Online survey study	Adults with dementia-related illness (ie, Alzheimer's disease, frontotemporal lobe dementia, vascular dementia)	Family caregivers (N=23) • 94.7% partners/spouses	PCL-C	26.1%
O'Donnell et al, 2022 (USA) ³⁸	Prospective, cross-sectional, multisite study	Adults with multiple myeloma	Family/friend caregivers (N=127) • 68.5% partners/spouses	PCL	24.4%
Liang et al, 2019 (USA) ¹³	Single-center, cross-sectional study	Adults undergoing hematopoietic cell transplant recipients	Informal caregivers (N=333)	PCL-5	6.6%
Jia et al, 2015 (China) ¹²	Single-center, cross-sectional study	Adults with acute leukemia, including acute lymphoblastic leukemia and acute nonlymphoblastic leukemia/ acute myelocytic leukemia	Family caregivers (N=163) • 52.1% partners/spouses	PCL-C	36.8%
Teixeira et al, 2013 (Portugal) ³⁹	Multicenter cross-sectional study	Adults with cancer requiring chemotherapy	Adult children caregivers of parents (N=214)	IES-R	40%
Studies in Caregivers of Pediatric Patients					
Cesa et al, 2022 (USA) ⁴⁰	Single-center, cross-sectional study	Children with inflammatory bowel disease	Parents of patient (N=155)	IES-R	8%
Roorda et al, 2022 (The Netherlands) ⁴¹	Single-center, cross-sectional study	Infants and toddlers with congenital gastrointestinal malformations	Parents of patient (N=79)	SRS-PTSD	16.5%
Beaudoin et al, 2021 (Canada) ⁴²	Single-center, cross-sectional study	Pediatric neurosurgical patients	Primary caregiver (N=168) • 82% mothers	PCL-5	44.6%
Carmassi et al, 2020 (Italy) ⁴³	Single-center, cross-sectional study	Children with epilepsy	Parents of patient (N=100)	SCID-5	25%
Schecter et al, 2020 (USA) ⁴⁴	Single-center questionnaire study	Infants discharged from the NICU (N=91)	Parents of patients	PCL-C	15%
Carmassi et al, 2019 (Italy) ⁴⁵	Single-center, cross-sectional study	Children with epilepsy (N=199)	Parents of patient	SCID-5	15.7%
Delozier et al, 2019 (USA) ⁴⁶	Multicenter cross-sectional study	Infants with disorders of sex development	Parents of patient (N=93)	IES-R	13.5%
Kim et al, 2015 (Korea) ¹⁴	Single-center prospective study	Infants discharged from the NICU	Mothers of patients (N=130)	PPQ	22.2% to 25%
Franck et al, 2014 (UK) ⁴⁷	Single-center prospective study	Children hospitalized on general pediatric wards	Parents of patient (N=253)	IES-R	21.5%
Bronner et al, 2010 (The Netherlands) ⁴⁸	Prospective longitudinal study	Previously healthy children unexpectedly admitted to the PICU admission for an acute, life-threatening medical event	Parents of patient (N=190)	SRS-PTSD	12.6% at 3 months 10.5% at 9 months
Lefkowitz et al, 2010 (USA) ⁴⁹	Single-center prospective study	Infants in the NICU	Parents of patient (N=130)	PCL	Mothers: 15% Fathers: 8%
Studies in Mixed-Age or Age-Not-Reported Populations					
Baum et al, 2022 (USA) ⁵⁰	Single-center, cross-sectional study	Patients aged 15 to 39 years with a newly diagnosed primary cancer	Caregivers (N=37) Majority were spouses (64%) and parents (27%)	IES-R	52%
Bos-Roubos et al, 2022 (The Netherlands) ⁵¹	Questionnaire study	Children and adults with Prader-Willi syndrome	First- and second-degree relatives (N=98)	PCL-5	12.1%
Richardson et al, 2016 (New Zealand) ⁵²	Single-center, prospective study	Patients with head and neck cancer (age not specified)	Family/friend caregivers (N=78) 63% partners/spouses	PSS-SR	19%
Rady et al, 2021 (Egypt) ¹⁵	Cross-sectional, comparative, observational study	Patients with severe mental illness (age not specified)	Family caregivers (N=70) 51.5% parents	PDS	15.17%

CIDI, indicates Composite International Diagnostic Interview; HTQ, Harvard Trauma Questionnaire; IES, Impact of Event Scale; IES-R, Impact of Event Scale – Revised; PCL, PTSD Checklist; PCL-5, PTSD Checklist for DSM-5; PCL-C, PTSD Checklist – Civilian; PC-PTSD, Primary Care PTSD Screen; PDS, Posttraumatic Diagnostic Scale; PPQ, Perinatal Post Traumatic Stress Disorder Questionnaire; PSS-SR, PTSD Scale-Self Report; PTCL, The Posttraumatic Cognitions Inventory; PTSD, posttraumatic stress disorder; PTSS-10, Posttraumatic Symptom Scale-10; SCID-5, Structured Clinical Interview for the DSM-5; SLR, systematic literature review; SRS-PTSD, Self-Rating Scale for PTSD.

^aData from 3 studies have been omitted from this table; 2 studies included participants that were inconsistent with the target population, 1 study did not separate PTSD prevalence from other trauma-related disorders

^bClinically significant PTSD. ^cOne participant in this study was classified as a formal caregiver.

Figure. Calculation of annual excess direct healthcare costs attributable to PTSD in the US population of family/friend caregivers



^aWhile the AARP and NAC report a total of 53 million US caregivers for 2020, this estimate broadly includes anyone “having provided care to an adult or child with special needs at some time in the past 12 months”.¹ To derive an estimate more representative of the population at risk for PTSD as described by the DSM-5-TR diagnostic criteria elucidated above, we utilized 50% of the total population, informed by the proportion of caregivers whose care recipient was hospitalized over the previous 12 months (48%; reported by the AARP and NAC), for an at-risk population of 26.5 million.¹

^bAnnual cost estimates were adjusted to 2020 USD using the US Consumer Price Index for medical care. AARP indicated American Association of Retired Persons; NAC, National Alliance for Caregiving; PTSD, posttraumatic stress disorder; US, United States; USD, United States dollar.

diverse; the studies came from multiple countries/regions, and many were small, single-center studies. Thus, the model presented here assumes that the PTSD prevalence estimates identified in our literature review are applicable to the overall population of family/friend caregivers in the United States. Further, our analysis assumes that PTSD in family/friend caregivers incurs similar direct healthcare costs to other types of PTSD in US civilian populations. While these assumptions warrant further refinement, the magnitude of the preliminary cost figure—compounded by the steady growth of the caregiving population—underscores the need for further study to drive practice and policy.

Earlier in this report, we recognized the need to contextualize the caregiver population in the greater landscape of literature on PTSD, particularly in studies that report economic data. While the type of traumatic event and the severity of PTSD symptoms have both been found to influence economic outcomes, none of the studies we reviewed suggest that caregivers experience a mild form of PTSD relative to other sufferers.^{21,26}

In fact, the diagnostic criteria utilized in most of the prevalence studies require PTSD symptoms of moderate to high severity. Serious outcomes associated with PTSD such as suicidal ideation and substance abuse have similarly been reported in the family/friend caregiver population.²⁷⁻³¹

Annual excess direct healthcare cost of PTSD in the caregiving population of more than \$74 billion USD for 2020.

Moreover, while trauma-related outcomes are influenced by factors such as social and economic resources, age, gender, education level, personality and worldview, etc, posttraumatic trajectories of family/friend caregivers have been found to be consistent with those of the general population of individuals who experience a traumatic event.^{14,32,33} While these initial findings provide some insight, further study is needed to fully understand the place of the family/friend caregiver in the PTSD landscape,

and to investigate whether there are any substantial differences relative to other populations for whom PTSD costs and outcomes have been reported.

Conclusion

Given that receiving a mental health diagnosis is associated with a dramatically increased likelihood of receiving appropriate treatment, the implications of PTSD underdiagnosis are grave; a lack of appropriate treatment has been linked to adverse outcomes including an increase in suicide attempts, greater impairments to QoL, and high healthcare costs, among others.¹⁹ Further, as the excess cost drivers in the 2 economic studies were primarily related to the use of medical services (including inpatient and outpatient services, other medical, and pharmacy costs), early intervention and treatment of PTSD have the potential to reduce the overall cost burden associated with this diagnosis. The substantial role that family/friend caregivers play in healthcare systems across the globe demonstrates the critical importance of their health and well-being, and recent recommendations suggest the implementation of educational and screening programs targeted at recognizing and treating mental health disorders in this population.^{14,20} By characterizing the economic burden of one common yet underrecognized diagnosis in these individuals, we hope to add to the existing body of research and help move the dial towards a more thorough integration of these recommendations into clinical practice and policy.

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