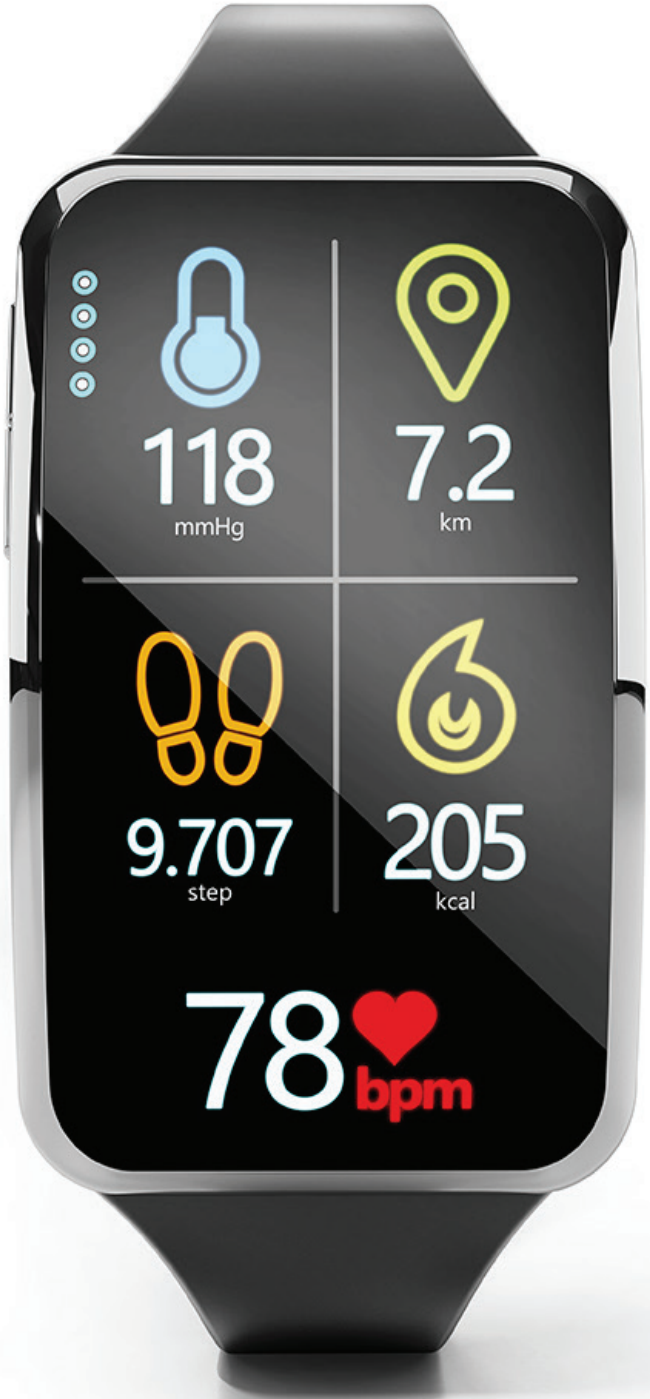
MARCH/APRIL 2024 VOL. 10, NO. 2

VALUE & OUTCOMES SPOTLIGHT

A magazine for the global HEOR community.

Defining Digital Health & Getting Clarity for HEOR



ISPOR
Improving healthcare decisions

VALUE & OUTCOMES SPOTLIGHT

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A magazine for the global HEOR community.

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

ISPOR
Improving healthcare decisions

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FROM THE EDITOR

Digital Health: Bridging the Gap Between Technology and Outcomes

In an era where they permeate every aspect of our lives, technology and digitalization have also revolutionized healthcare. Digital health is the term coined for the convergence of digital innovation and health services. But what exactly is digital health and how does it affect health outcomes and healthcare policy?

Digital health encompasses a broad spectrum of technologies, applications, and services that leverage digital tools to enhance health and wellness. From wearable fitness trackers to telemedicine platforms, the digital health ecosystem is vast, dynamic, and ever-expanding. As examples, digital health includes mobile health apps, electronic health records (EHRs), remote monitoring devices, and artificial intelligence-driven diagnostics—just to name a few.

> The positive effects of digital health on patient outcomes are multifaceted. Digital health has the potential to empower individuals to take charge of their own health.

The positive effects of digital health on patient outcomes are multifaceted. First and foremost, digital health has the potential to empower individuals to take charge of their own health. Mobile apps provide personalized health information, track physical activity, and offer reminders for medication adherence. Patients can access their EHRs, view test results, and communicate with healthcare providers seamlessly. This empowerment leads to better self-management and thus improved health outcomes.

As we have discussed in a previous issue of *Value & Outcomes Spotlight*, wearable devices and health sensors collect real-time data on vital signs, sleep patterns, and activity levels and may allow for early detection and prevention of medical issues. By analyzing this data, healthcare professionals can identify early warning signs of diseases such as diabetes, hypertension, or sleep apnea. Timely interventions can prevent complications and improve overall health.

Digital health also enables virtual consultations, telemedicine, and remote consultations. Patients can consult specialists from the comfort of their homes, reducing travel time and enhancing access to healthcare. Telemedicine also facilitates follow-up care, reducing readmission rates.

> Digital health is not a futuristic concept–it is reality today. As we navigate this digital frontier, policy makers, healthcare providers, and patients must collaborate to harness its potential.

Advances in genomics and data analytics allow for personalized treatment plans and medicines. Digital tools analyze genetic information, predict drug responses, and tailor therapies based on an individual's unique profile. Precision medicine of this kind improves treatment efficacy and minimizes adverse effects.

Health apps can encourage positive behaviors. Whether it's quitting smoking, managing stress, or maintaining a healthy diet, digital interventions provide reminders and educational content that can lead to behavioral changes critical for preventing chronic diseases.

The rise of digital health also presents new challenges that healthcare policy must address. These include ensuring data privacy and cybersecurity, as well as promoting

equitable access to digital health technologies. Healthcare policies need to be robust and flexible, capable of protecting patients in a digital age while also fostering innovation. Policy makers are tasked with the complex job of balancing these needs. They must create regulations that safeguard patient information and ensure the security of digital health platforms, while also promoting a fair digital health environment where all individuals, regardless of their socioeconomic status, can benefit from the advancements. The successful integration of digital health into healthcare policy has the potential to create a more responsive and effective healthcare system, ultimately leading to improved health outcomes.

In conclusion, digital health is not a futuristic concept—it is reality today. As we navigate this digital frontier, policy makers, healthcare providers, and patients must collaborate to harness its potential. By embracing digital health thoughtfully, we can improve health outcomes, enhance patient experiences, and create a more resilient healthcare system for all.

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

The Digital Transformation of Health

Rob Abbott, ISPOR CEO & Executive Director

It's no exaggeration to suggest that the healthcare industry is in a state of disruption. Its business infrastructure is being leapfrogged as society moves toward digital channels for information, transactions, and interactions. In the wake of the COVID-19 pandemic, patients have more agency and self-determination and expect high-quality care that is accessible, effective, efficient, and affordable. These expectations are driving healthcare systems to confront digital technologies that will transform current care models, business processes, and patient and member experiences.

It is in this context that I welcome this issue of *Value and Outcomes Spotlight* that is dedicated to exploring the digital transformation of health. It is appropriate to define "digital transformation" for our purposes here. It is the practice of using technology to add value to patients and healthcare organizations in a way that, at least in theory, maximizes benefits for both. Popular examples include the seemingly ubiquitous "wearable technologies" (Fitbit, anyone?) and the development of the infrastructure needed to support telehealth and other remote, virtual healthcare solutions.

Technological innovation has become an integral part of our lives. Whether booking a hotel or airfare, watching a movie, or buying something for the house, we increasingly use devices of various types to get things done. It's sometimes hard to believe that companies like Amazon, Apple, and Alphabet (parent company of Google), which dominate the Fortune 500, are all very young – Google's IPO, for instance, was in 2004. In a healthcare context, wearable technologies that track a variety of health metrics, the onset and rapid acceleration of telehealth, and the creation of "patient portals" that provide useful information for both the patient and the doctor are all expressions of the digital transformation of healthcare.

And there is so much more to come.

By 2025, according to research by Global Market Insights, the world's digital healthcare market is expected to be worth more than $500 billion annually. If nothing else, this is a strong signal of the potentially transformative impact technology can bring to healthcare. Meantime, research by Deloitte Insights shows that patients are increasingly exercising greater agency, engagement, and control over most decisions about their health and well-being[i].

To be sure, there is considerable opportunity to transform healthcare through technologies already in the market, and many others that are in various stages of deployment. The use of artificial intelligence to automate record keeping or refine predictive diagnostics and the creation of patient treatment plans is a topical example that is discussed in this themed issue of *Value & Outcomes Spotlight*. So too, the development and deployment of medical robots to perform complex surgeries. As noted in a recent paper by Sakshi Bramhe and Swanand Pathak[ii], robotic surgery "is commonly done in the surgical community to an incredible level." The use of 3D printing to create prosthetics, big data to create patient profile and/or treatment plans, and cloud computing to help deliver remote healthcare are other examples of the digital transformation of healthcare.

The putative benefits of digital solutions are many—for both providers and patients—and include:

Provider Benefits:

- reduced time for patient examination
- more effective remote communication between doctors and patients
- more efficient communication between medical staff
- creation of a secure database for electronic medical records

Patient Benefits:

- access to personalized healthcare services
- real-time tracking of health metrics
- access to personal health records
- more convenient appointment scheduling

Lest we view the digital transformation of healthcare with the proverbial rose-colored glasses, it is important to note some of the challenges that might otherwise get in the way of wide adoption of new technologies. These include data privacy and security; the historic inertia that makes healthcare organizations resistant to change; interoperability issues that make it difficult, if not impossible, to marry legacy systems with new digital applications; and the challenges of bringing new IT skills and talents to doctors and other healthcare providers. Some of these challenges are also discussed in this issue of *Value & Outcomes Spotlight*.

At ISPOR, we increasingly strive to leverage our experience and expertise in health economics and outcomes research to help forge a world in which healthcare is accessible, effective, efficient, and affordable for all. A critical part of this is rigorously examining the value of new technologies. With this in mind, the articles in this issue of *Value & Outcomes Spotlight* serve as both a sign of things to come, and equally, a signal of our intent to continue "bringing the horizon into the room" and commenting on the efficacy of new ideas and technologies.

[i] https://www2.deloitte.com/us/en/insights/industry/health-care/digital-transformation-in-healthcare.html

[ii] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9573327/

No Easy Predictions About the European Union Joint Clinical Assessment

Christiane Truelove

Signal

IN BRIEF

- In considering the potential PICO burden, an analysis looking at a hypothetical non-small cell lung cancer product came up with 10 PICOs, potentially requesting a minimum of 280 analyses
- The EUnetHTA 21 guidelines are striving for inclusivity and independence for Member States. Member States will need to define what comparators, populations and outcomes are relevant for them.
- Health technology developers are asking for early and meaningful engagement with HTA bodies and predictability in the PICO consolidation process.
- HTA bodies will need to start assessment scope considerations for PICOs much earlier than they are today.

In January 2025, the European Union (EU) HTA Regulation will be applied and start with a phased use of a standardized framework – the Joint Clinical Assessment (JCA) – which all of the 27 Member States will use to evaluate new medicines or medical devices. By reducing redundant practices and introducing a single transparent process, the hope is that the JCA speeds the introduction of innovative technology to patients all across Europe.

The EUnetHTA 21 joint consortium wrapped up its work in September 2023. A special spotlight session at ISPOR's Europe meeting, EU Joint Clinical Assessment: One for All and All for One in November 2023 examined ways that PICOs [population, intervention, comparator, and outcomes] could be consolidated, presenting perspectives from EUnetHTA 21, government, and health technology developer on the proposed process, methodology, and implications for evidence development. The intent of the session was to address the question of how to develop a JCA scoping procedure that has the most impact and brings value to EU patients.

"I have a dream," said James Ryan, who represents AstraZeneca on regional and global HTA Policy around the world and is a co-lead on the European Federation of Pharmaceutical Industries and Associations health technology assessment (HTA) Working Group's methodology workstream on the EU HTA Regulation. "Imagine what a world-class HTA system would look like. What principles should drive it? How can it make the most impact for patients in a resource-constrained world? Right now the EU has that unique opportunity to develop, implement, and actually deliver the #1 HTA system in the world—one is of high quality, scientifically credible, transparent, and inclusive."

Ryan dreams about having improved and more equitable patient outcomes across Europe, where decision making is quicker, European evidence needs are prioritized, uncertainty is reduced, and the return on Member States' constrained resources are maximized across all stakeholders. "Who among us wouldn't want that? And yet despite this, I don't actually sleep well," Ryan said. "In fact, the proposals put forward by EUnetHTA 21 often keep me up at night. I dream PICOs."

Defining and Understanding How PICOs Could Work

While EUnetHTA 21 has outlined an approach for the PICO scoping process, it's only a proposal until the EU adopts the JCA implementing act, currently under consultation, and the Coordination Group finalizes scoping guidance. Under the proposed process, the health technology developer begins by submitting a regulatory dossier to the European Medicines Agency (EMA).

Then the assessors will receive the anticipated label and use that information to propose one or multiple PICOs, which is sent out as a survey to all 27 Member States. In the survey, the Members would comment on whether they would agree with the PICO(s) as laid out by the assessors or whether they have other national needs. The assessors would then consolidate all these surveys and come up with the lowest number of PICOs possible, yet enough to meet the needs of all 27 Member States. According to Van Engen, this will result in PICOs with one population, one intervention and one comparator. In the final steps, the EUnetHTA 21 scoping guidance outlines that all the outcomes as requested by the Member States are applied to each PICO and then the PICO would be validated before the consolidated PICO is shared with the health technology developer.

KEY TAKE-AWAYS

- EUnetHTA 21 state all Member State needs must be translated into the PICOs, which should not be data driven but based on policy needs.
- There is a lack of guidance for Member States on how to select comparators and populations for their PICOs.
- Health technology developers argue that these policy needs should be informed by evidence on current clinical practice, and require predictability in how PICOs will be consolidated beyond what is currently proposed.
- Member States will need to start earlier and change their process to inform the PICO survey.

Anke van Engen, managing principal at IQVIA in Amsterdam and leader of the Health Economics/HTA Center of Excellence in the European Value & Payer Evidence practice, led IQVIA's case study simulating the PICO for a hypothetical product in non-small cell lung cancer to determine what the potential PICO burden could be like. "In non-small cell lung cancer, there were 11 EMA products approved at the time that we did our analysis. The latest product that was approved was nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy. We assumed that 'Product X' had an equivalent trial design as nivolumab and used the same patient population, same comparator, and the same study endpoints. We then looked at the clinical guidelines, the ESMO (European Society for Medical Oncology) guidelines, and national clinical guidelines, as well as the latest HTA reports," Van Engen said.

Six of the 27 Member States had a published an HTA report on nivolumab. "Based on this information, we anticipated what each Member State of each country that has an HTA report would fill in for their country-specific PICO(s) and then we applied the EUnetHTA scoping process guidance to come up with consolidated PICOs," Van Engen said. After consolidating the PICOs, IQVIA came up with a minimum of 10. "We had 9 different populations, 9 comparators. About 5 of the 10 PICOs could be addressed by head-to-head data, yet the other 5 would require indirect treatment comparisons." Additionally, across the 6 countries that asked for the 5 PICOs, there were 28 outcomes requested—14 clinical outcomes, 9 safety outcomes, and 5 health-related quality-of-life outcomes.

Applying 28 outcomes to all 10 PICOs would result in a total of 280 requested analyses, "assuming there's only 1 outcome measure and no subgroups requested," Van Engen points out. But the complexity can grow "exponentially" if, for example, an additional outcome measure or more subgroups, or more detailed safety endpoints are requested. Additionally, when IQVIA included the National Institute for Health and Care Excellence (NICE) in the United Kingdom, an HTA body often referred to by other HTA bodies, the PICO numbers would increase from 10 to 14.

EUnetHTA and Health Technology Developer Views

According to Anne Willemsen, who works for the Dutch National Healthcare Institute (Zorginstituut Nederland) and is now the Co-Chair of the JCA subgroup, the key principles behind EUnetHTA 21 guidance are around inclusiveness and independence. Inclusiveness specifically means all Member State needs have to be translated into the PICOs, and independence means that the PICO should not be data driven but has to be based on policy needs. "I think this is where the controversy lies. But for us it is really important that we come up with a PICO definition that comes from our policy question regardless of what is being studied," Willemsen said. "We know and we accept there may be questions that cannot be answered. But for us it is important to have those outlined." The population in the PICO would either be the full patient population or subpopulations defined as part of the full population. Willemsen added that Member States need to be as detailed as they can, "because this is really critical information, we need to be able to consolidate the PICO in the end."

Willemsen stressed that the Member States need to CLEARLY define what comparator is relevant for them. "The standard of care is often different in each country, therefore we need Member States to specify this in detail," she said. She added that one of the important learnings in EUnetHTA 21 was finding out each country and HTA body may use terms differently.

According to Ryan, the more than initially predicted number of PICOs in the test study and the lack of engagement and evidence-based guidance on how to develop PICOs at a Member State level are causes of concern for health technology developers. "That produces uncertainty for us all. It leads to variation and

duplication across Europe. And what the HTA bodies tell us about uncertainty—they don't like it," Ryan said.

Ryan noted the EUnetHTA 21 process proposes an "exponential number of analyses," with potentially more complex indirect comparisons, which he believes will be the norm and not the exception. He refers to this "analysis paralysis." As part of the solution, Ryan calls for HTA bodies to have "early and meaningful engagement" with health technology developers that should take into account the data health technology developers collect about a disease, the disease context, clinical practice across all Member States, and endpoints. "Why would a HTA process not want to capture that as part of their thinking? They've got to remain independent, but it's evidence. Engagement and sharing evidence will also reduce duplication for us, and it can increase trust across the whole process down to Member States and, ultimately, to patients," said Ryan. Health technology developers could also propose a PICO to help as a starting point.

By reducing redundant practices and introducing a single transparent process, the hope is that the JCA speeds the introduction of innovative products to patients all across Europe.

Ryan criticized the lack of guidance for Member States on how to select comparators and populations. "We have guidance on how to interpret data on subpopulations and subgroups, but not in how you go about selecting them for the PICO process. Simply put, the JCA population should be clinically relevant and actionable at a Member State level. If we're asking things that aren't clinically relevant, that's an inefficiency. It's a waste of resources. Ideally, those should be based on prespecified analyses and trial protocols or on clinical consensus. We should avoid subgroups that are not actionable or actually ignored," Ryan said.

Ultimately, not all analyses should have the same weight. "We should prioritize those that are required based on evidence and clinical relevance and focus on where most EU patients are covered," Ryan added.

Getting PICOs Off the Ground in Denmark

Kim Helleberg Madsen, director of pharmacoeconomics and availability of medicines at the Danish Medicines Agency, noted that due to the complex healthcare system in Denmark (which is composed of 4 bodies dealing with decisions in the primary healthcare sector, hospital medicines, medical devices, and vaccines), "we have a lot of coordination to do when it comes to implementing the JCA."

At the moment, the primary focus is on the methodology and procedural guidelines that are in the pipeline. "The scoping process guideline will be a key document in order to define what we are going to do in terms of PICOs that reflect the clinical practice in Denmark," Helleberg Madsen said.
He noted that at present, the Danish Medicines Agency receives reimbursement applications for the outpatient sector without any sort of predefined scope. "But health technology developers can reach out and pose questions regarding the assessment scope."

The Danish Medicines Council receives a request for an assessment from the health technology developer concerning medicines in the in-patent sector which includes a suggestion regarding PICO. However, if the PICO does not correspond to Danish clinical practice, the health technology developer will be informed about this prior to submission of their application.

Throughout the process, the Danish Medicines Council can request additional information. "I think one of the things that we would say in terms of the scoping process, we have to start our assessment scope consideration and have to look into the PICOs at a much, much earlier stage than we are doing today," Helleberg Madsen stated.

He added that there is also a question of how the EU will fund assessments at the Member State level. "I think our main concern at the moment is to arrive at implementing rules and guidelines that are workable—both for the health technology developers and the HTA bodies—so that we can arrive at a smooth and effective implementation of the HTA regulation."

Suggested Reading

- European Health Technology Assessment: Historical Success of European Joint Assessments
- Analyzing Indirect Treatment Comparisons in EUnetHTA Assessments: Lessons Learned for the Implementation of EU Joint Clinical Assessments?

About the author

Christiane Truelove is a freelance medical writer based in Bristol, PA.

FROM THE JOURNALS

Logical Inconsistencies in the Health Years in Total and Equal Value of Life-Years Gained

Paulden M, Sampson C, O'Mahony JF, et al. *Value Health*. 2024;27(3):356-366
Section Editor: **Agnes Benedict**

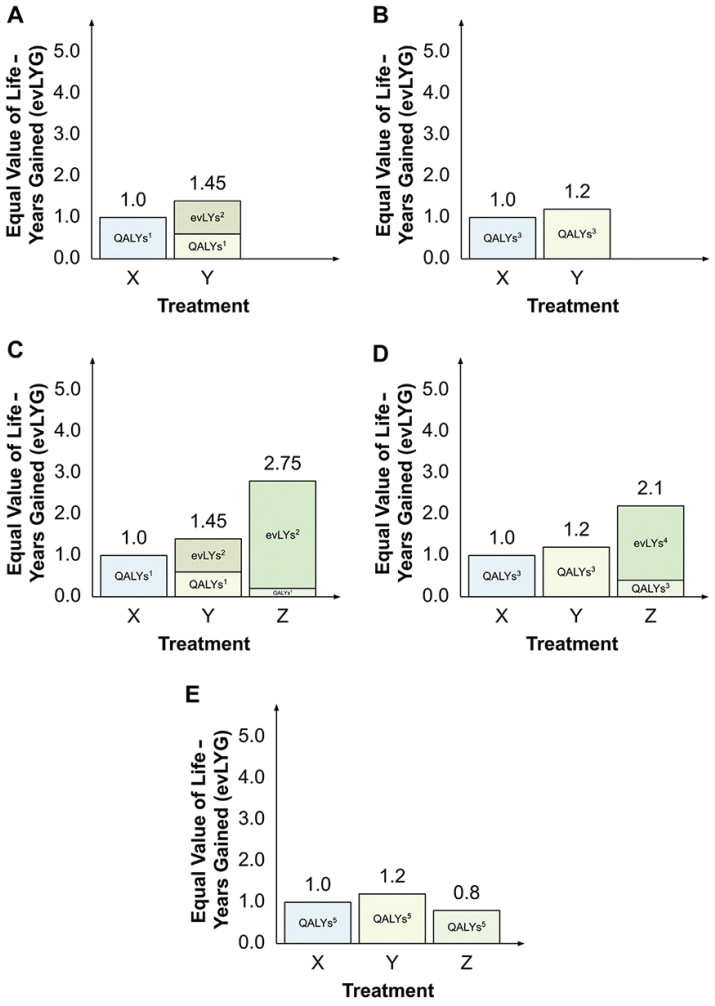
The quality-adjusted life-year (QALY) has been the standard measure in economic evaluations and is used widely in many health technology assessment (HTA) countries for decision making. The use of QALY is subject to much criticism and an ongoing debate since its inception several decades ago. The controversy is reflected by the title of Milton Weinstein's 1998 paper entitled, "A QALY Is a QALY Is a QALY—Or Is It?"[1] The answer by many is that it is not. There is evidence that an improvement brought about for patients who generally have poor quality of life may be valued more by society than their healthier counterparts. However, since the same extension of life is weighted by a lower health utility, in the standard QALY framework that will not be true. Recent years have seen proposals for alternative approaches, including the equal value of life-years gained (evLYG)[2] and "health years in total" (HYT).[3] These are actively discussed by HTA bodies and evLYG calculation is considered by the Institute for Clinical and Economic Review. However, due to their recency, a lot less general knowledge and experience have been accumulated among members of the health economics and outcomes research (HEOR) community[4] with these approaches, compared to the QALY approach.

The paper by Paulden and colleagues summarizes these new proposed methods and provides step-by-step illustrations of how to calculate both measures through simple examples that involve comparisons of mutually exclusive treatment options that can achieve 3 different life expectancies with different quality of life.

The paper then compares the 2 new approaches to each other and to the classic approach of comparing technologies using QALYs and life years only. The authors point to some logical inconsistencies in decision making by applying the new methods. The evLYG approach, the authors suggest, can result in decision instability, since the preferred decision depends on what is considered current standard of care. As illustrated in the **Figure** below, the choice among 3 therapies X, Y, and Z will depend on which one is considered standard of care. When only X and Y are available, Y is always preferred (panels A and B). When Z is the new treatment and either X or Y is standard of care, Z will be preferred (panels C and D). However, if Z becomes the standard of care and a reassessment takes place, preference ordering of the original 2 treatments may change (from Z to Y), as shown in panel E.

The authors also show that the HYT violates the basic axiom of rational choice theory of "independence of irrelevant alternatives." Under certain circumstances, if a new, mutually exclusive option of treatment C becomes available, the preferred choice between treatment A versus treatment B may change.

Figure. evLYG for each treatment, assuming (A) treatment Z is not available and treatment X is current treatment; (B) treatment Z is not available and treatment Y is current treatment; (C) treatment Z is available and treatment X is current treatment; (D) treatment Z is available and treatment Y is current treatment; or (E) treatment Z is available and treatment Z is current treatment.



Notes: [1]Quality-adjusted life-years (QALYs) calculated over year 1 only. [2]Equally valued life years (evLYs) calculated from year 2 onwards. [3]QALYs calculated over years 1-2 only. [4]evLYs calculated from year 3 onwards. [5]QALYs calculated over all 4 years.

This may result in inconsistent social decision making. Other important practical and theoretical concerns with the method of HYT are summarized, including (but not restricted to) its capacity to handle heterogeneity and the plausibility of separating the value of life expectancy and the value of a certain health-related quality of life.

The paper fills a gap for members of the HEOR community by providing an overview of the background to each proposal, by explaining and comparing the new approaches in easy-to-follow terms through some simple examples. The challenges with their applications are explained in terms of real situations HTAs may face. The paper then closes with a proposal for an alternative that is free of logical inconsistencies: that of equity-weighted QALYs that can address the original issue with the QALY-based approach, while meeting the axioms of rational decision making. The authors highlight that equity weighting is not straightforward to do properly and provide references to past research in the area. For anyone interested in this fundamental question in health economics, this paper is strongly recommended.

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ISPOR Conferences and Events

ISPOR 2024 | May 5-8
Georgia World Congress Center, Atlanta, GA, USA

HEOR: A Transformative Force for Whole Health

Be there next month when experts from all areas of healthcare gather at the Georgia World Congress Center, Atlanta, GA, USA, for ISPOR 2024, the leading global conference for health economics and outcomes research (HEOR). Be sure to add the Digital Conference Pass to your registration to access recordings of nearly all educational sessions.

Mark your calendar for these plenary sessions:

Monday, May 6 | 8:30AM EDT

Advancing Whole Health: How do We Know When We're Succeeding?

Tuesday, May 7 | 8:30AM EDT

Missing Link for HEOR: A Path Forward for HEOR Data Integration

Wednesday, May 8 | 11:30AM EDT

AI Enabling Whole Health: Opportunities and Challenges for HEOR and HTA

The following is a sampling of sessions and hot topics from across the HEOR spectrum:

Health Policy and Regulatory
Medicare Drug Price Negotiation: Lessons from the First 10 Drugs Selected [Spotlight session]

Economic Evaluation
How to Adjust Economic Models for Health Equity in the Conduct of Generalized Cost-Effectiveness Analysis [Spotlight session]

Methodological and Statistical Research
Unlocking the Potential of Open Source Models: Strategies to Navigate Barriers in Development and Adoption [Forum]

Patient-Centered Research
Including the ISPOR Patient-Centered Research Summit 2024 [co-located at ISPOR 2024 | May 5]

Real-World Evidence
Revolutionizing Regulatory Pathways: Unleashing the Power of Real-World Evidence, Adaptive Trials, and Synergistic Collaboration for Expedited FDA Device Approval, Breakthrough Designation, and CMS Reimbursement [Panel session]

Pre-conference Short Courses
A full day of short courses will be held on May 5. The ISPOR Short Course Program is designed to enhance knowledge and techniques in core HEOR topics as well as emerging trends in the field. Taught by expert faculty, courses span across 7 topical tracks and range in skill level from introductory to experienced.

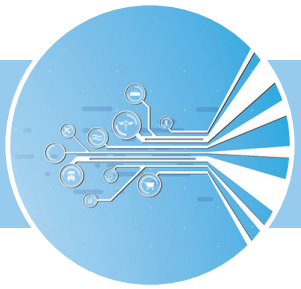
More at www.ispor.org/ISPOR2024

Join the conversation on Twitter #ISPORAnnual

ISPOR Conferences and Events

ISPOR Patient-Centered Research Summit 2024 | May 5

Georgia World Congress Center, Atlanta, GA, USA



A co-located event at ISPOR 2024, this year's Summit theme is "Advancing Patient-Centered Research." The half-day Summit promises to be an enriching and informative gathering of experts, researchers, and practitioners in the field, where we will explore the latest advancements, emerging standards, and breakthroughs in patient-centered research. Attendees can engage in dynamic discussions on strategies, regulatory policies, and methods that enhance the influence of patient involvement in generating evidence and shaping healthcare decisions.

Sessions include:

The Power of Patient Voices: Elevating Patient-Centered Outcomes in Research

Making a Difference: Identifying Best Practices to Measure the Impact of Patient Engagement

Patient-Centered Methods: Accomplishments, Innovations, and the Future

Advancing Patient-Centered Research: Seizing Opportunities and Addressing Challenges

Learn more about the Summit and register here.

Call for Abstracts!

ISPOR Europe 2024 | 17-20 November
Barcelona International Convention Center, Barcelona, Spain

Mark your calendars for ISPOR Europe 2024, the leading European conference for health economics and outcomes research (HEOR) this 17-20 November! Network with your peers, HEOR experts, and thought leaders. Submit your issue panel, workshop, other breakout session or case study abstract for an opportunity to interact and discuss your innovative experiences in outcomes research with a global audience. Research submissions open 18 April. Submit today!

SUBMIT AN ABSTRACT

The Call for Abstracts Submission Windows for ISPOR Europe 2024:

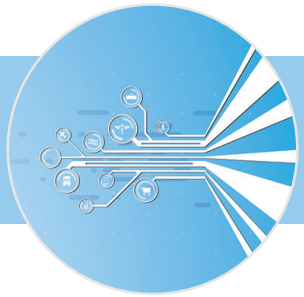
	Abstract Submissions Open:	*Abstract Submissions Close:*
Issue Panels, Workshops, Other Breakout Sessions, Case Studies	28 March	6 June
Research	18 April	27 June

Details at www.ispor.org/ISPOREurope2024

Join the conversation on social media using the official conference hashtag #ISPOREurope

Get in front of your target audience and ensure your company is included in the conference Exhibitor Guide! Contact sales@ispor.org.

ISPOR Real-World Evidence Summit 2024 | 17 November
Barcelona International Convention Center, Barcelona, Spain



A co-located event at ISPOR Europe 2024, the 17 November Summit will the cover latest developments in use of real-world evidence (RWE) across the regulatory health technology assessment-payer decision-making continuum with a focus on methods, data transportability, and infrastructure. Major topics to be covered include causal inference and external control arms for comparative effectiveness analyses, the hierarchy of RWE studies, and the role of patient registries. The use of RWE in Joint Clinical Assessment of the EU HTA regulation will be explored, with insights from the cross-border collaborations on pricing and reimbursement in the EU countries. In addition, the feasibility of HTA reassessment post market entry will be considered, drawing from lessons learned from US Medicare Drug Price Negotiation.

Save the Date!

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- Discuss cutting-edge technologies shaping the future of clinical research, from Natural Language Processing to AI-driven analytics.
- Identify practical strategies for integrating RWE and technology to optimize trial efficiency and outcomes.

May 20 | 10:00AM – 11:00AM EDT

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- Benefit from live demonstrations of several pioneering AI-driven platforms designed to optimize and expedite systematic review processes.
- Acquire practical insights into the applications of AI, understanding how these platforms enhance efficiency, accuracy, and overall effectiveness in systematic reviews.

May 22 | 10:00AM – 11:00AM EDT

The Global Socioeconomic **Impact** of Rare Diseases: A Call for Action

By completing this webinar, you will:

- Gain an understanding of studies conducted in high-income countries, and the impact of data scarcity in lower- and middle-income countries on the socioeconomic estimates.
- Understand the consequences of low investment in rare diseases on the overall burden.
- Learn to gauge the value of investing in diagnosis and early interventions.

May 28 | 10:00AM – 11:00AM EDT

The Role of RWE for Devices and Diagnostic Market Access in Europe

By completing this webinar, you will:

- Understand country-specific key decision pathways for medical devices and diagnostics reimbursement and learn which of these requirements can be satisfied by real-world evidence (RWE).
- Be introduced to specific examples on how RWE was used to satisfy country-specific HTA hurdles.
- Understand the strengths and limitations of real-world data in the context of utility in reimbursement decision making.

May 29 | 10:00AM – 11:00AM EDT

Are Clinical Outcome Assessments Sufficiently Valued?

By completing this webinar, you will:

- Increase your awareness of the complexity in developing clinical outcomes assessment (COA) strategies to meet different stakeholder requirements.
- Develop a greater understanding of the value of COA data from diverse perspectives and identify synergies across the value of COA data among various stakeholders.
- Gain a greater awareness of various initiatives in development to enhance the value of COA data.

June 11 | 12:00PM – 1:00PM EDT

Overcoming the Barriers of Open-Source Modeling

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- Gain an understanding of why the uptake of open-source modeling (OSM) has been limited.
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HEOR NEWS

1 Medicare and Medicaid Open Coverage of Anti-Obesity Drugs for Heart Patients (Endpoints News)

The Centers for Medicare & Medicaid Services said that anti-obesity drugs should be covered for patients getting them for additional medical conditions, such as reducing the risk of major cardiovascular events. Read more

2 WHO to Begin Development of Parallel Recommendation and Regulatory Pathways; Shortening the Time Taken for People to Access Health Products (WHO)

To shorten time to access innovative health products in low/low-middle income countries, WHO is adopting its expedited, parallel prequalification and emergency usage list recommendation and review process—used during the pandemic for COVID-19 products—to all products, instead of continuing to do these processes sequentially. Read more

3 Abortion Law Emergency-Exemption Guidance Proposed by Texas Medical Board (STAT News)

The Texas Medical Board, responding to pressure from the state Supreme Court and widespread uncertainty among physicians, has proposed draft guidance in an attempt to clarify what constitutes emergency grounds for a legal abortion. Read more

4 WHO Launches New Toolkit Empowering Health Professionals to Tackle Climate Change (WHO)

The World Health Organization, in collaboration with partners, has developed a new toolkit designed to equip health and care workers with the knowledge and confidence to effectively communicate about climate change and health, by filling in the gaps in knowledge and action that will help them raise awareness, advocate for policy changes, and empower communities to mitigate and adapt to climate change. Read more

5 Perinatal Mood and Anxiety Disorders Rose Among Privately Insured People, 2008-2020 (Health Affairs)

Researchers found that perinatal mood and anxiety disorder (PMAD) diagnoses among privately insured people in the United States increased by 93.3% from 2008 to 2020, growing faster in 2015–2020 than in 2008–2014, and suggesting worsening morbidity in maternal mental health nationwide. Read more

6 Meals on Wheels Clients: Measurable Differences in the Likelihood of Aging in Place or Being Hospitalized (Health Affairs)

In looking at the likelihood of continued community residence and risk for hospitalization of elder Medicare beneficiaries, researchers found users and nonusers of home-delivered meals programs were equally likely to still reside in the community one year later but continued community residence was more likely among users than nonusers who were Black, were enrolled in Medicaid, or were frail. Read more

7 Charting an Evidence-Based Roadmap for WHO Global Traditional Medicine Centre Collaborations (WHO)

Experts from over 40 countries across all 6 WHO regions met in India to prioritize collaborations of the WHO Global Traditional Medicine Centre in efforts to evolve conventional research methods in studying personalized, holistic traditional medicine approaches, as well as evolving the global knowledge base through such methods as the development of a traditional medicine global library and a framework of intellectual property and other rights to ensure fair and equitable access and benefits. Read more

8 Cost-Effectiveness and Budget Impact of Decentralizing Childhood Tuberculosis Diagnosis in 6 High-Tuberculosis–Incidence Countries: A Mathematical Modeling Study (The Lancet eClinical Medicine)

Researchers assessed the cost-effectiveness and budget impact of decentralizing a comprehensive diagnosis package for childhood tuberculosis to district hospitals or primary health centers compared to standard of care in Cambodia, Cameroon, Côte d'Ivoire, Mozambique, Sierra Leone, and Uganda, and found that the district hospital-focused strategy may be cost-effective in some countries, depending on the cost-effectiveness threshold used for policy making. Read more

9 Effect of Single-Dose, Live, Attenuated Dengue Vaccine in Children With or Without Previous Dengue on Risk of Subsequent, Virologically Confirmed Dengue in Cebu, The Philippines: A Longitudinal, Prospective, Population-Based Cohort Study (The Lancet Infectious Diseases)

While the Philippine government suspended its children's vaccination program for 3-dose dengue vaccine because of safety concerns, researchers say a single dose of the vaccine did confer significant protection against hospital admission for virologically confirmed dengue among participants who had 2 or more previous dengue virus infections, compared with children who had none or 1 previous infection. Read more

10 Outcomes After Surgery for Children in Africa (ASOS-Paeds): A 14-Day Prospective Observational Cohort Study (The Lancet)

In looking at patient care and outcomes for children undergoing anesthesia and surgery in hospitals all across Africa, researchers determined these outcomes are poor, with complication rates up to 4-fold higher (18% versus 4·4–14%) and mortality rates 11-fold higher than high-income countries in a crude, unadjusted comparison (23·15 deaths versus 2·18 deaths per 1000 children). Experts call for health system strengthening, provision of safe environments for anesthesia and surgery, and strategies to address the high rate of failure to rescue. Read more

HTA POLICY UPDATE

Section Editors: **Sandra Nestler-Parr, PhD, MPhil, MSc; Ramiro E. Gilardino, MD, MSc**

Welcome to this new column that aims to inform about the latest policy changes, updates, and advancements in health technology assessment (HTA) and value assessment globally. This section serves as a centralized platform to share top-line news on how different healthcare systems are evolving their HTA policies and practices. While this feature primarily signposts to more detailed reports and analyses on HTA-related matters, it will discuss selected topics in more detail. We welcome suggestions for topics for this column from readers. Please contact the VOS editorial office with your suggestions.

Less than 300 days and counting: The EU Regulation on HTA

The Regulation on Health Technology Assessment in the European Union (EU HTAR; Regulation 2021/2282) entered into force in January 2022 and applies as of January 2025, initially to cancer therapies and advanced therapy medicinal products. From 2028, all novel orphan drugs will be subject to EU HTAR, followed in 2030 by all other drugs, in vitro diagnostics, and high-risk medical devices.

The main goal of EU HTAR is to enable the development of a joint perspective on clinical aspects of novel health technologies to facilitate accelerated and more equitable patient access to these technologies by increasing transparency and reducing duplication of assessment efforts. Harmonization of HTAs across the EU is expected to benefit smaller European countries with less-established HTA processes and promote regular collaboration among stakeholders.

The new framework covers joint clinical assessments (JCAs), joint scientific consultations (JSCs), the identification of emerging health technologies (horizon scanning), and voluntary cooperation. In the context of varying laws, policies, regulatory standards, and processes for HTA across 27 EU Member States, the implementation of the EU HTAR is a complex undertaking that presents both challenges and opportunities.

Under the new regulation, a JCA will be initiated shortly after a Marketing Authorization Application for a novel technology is filed to the European Medicines Agency (EMA). The JCA begins with a survey to collect information on population, intervention, comparator(s), and outcome(s) (PICOs) from all Member States, which forms the framework that defines the final scope of the JCA. The health technology developer must submit a dossier addressing the final PICOs 3 months in advance of the expected Committee for Medicinal Products for Human Use opinion.

While the assessment of clinical benefit compared to existing treatments will be centralized, subsequent appraisal of economic, social, and ethical aspects (ie, value considerations) remains a devolved matter, conducted at national level.

The mandatory EU HTA comes with some uncertainties for stakeholders. These include the complexity arising from evidence requirements to address multiple PICOs for the JCA and the constrained timelines between receipt of the final PICOs and submission deadline for the HTA dossier. Due to resource constraints at Member State and stakeholder levels, there is a question about how input will be elicited from clinicians and patients across all Member States within the stipulated timeframe.

Lack of clarity on specific aspects of the JCA process, timelines, and methods has resulted in much speculation over the past months. The long-awaited publication of the draft Implementing Act on Joint Clinical Assessments of Medicinal Products on 5 March 2024, providing procedural rules and methodological detail for the JCA of medicinal products, is an important milestone in the implementation of the HTA regulation. It includes details on the coordination of the JCA process within the EMA, engagement of stakeholders with the relevant expertise in the therapeutic area, the development of the assessment scope and timelines, the possibility of assessment scope explanation meetings for health technology developers, and the process for submission of new data from clinical trials to the EMA during the JCA and after publication of the JCA report.

The public consultation period for the draft Implementing Act on Joint Clinical Assessments of Medicinal Products closed on 2 April 2024. It is expected that questions and concerns were raised that indicate the need for further refinement and clarification to ensure the implemented legislation is comprehensive, robust, and effective.

The February 2024 update of the EU HTAR Implementation Rolling Plan outlines the current status of key activities undertaken by the European Commission in preparation for the implementation of Regulation 2021/2282.

Although preparation for the EU HTAR implementation deadline is underway across all stakeholder groups, there is still much to clarify and accomplish before full EU HTAR readiness is achieved.

RESEARCH ROUNDUP

Section Editor: **Aakash Bipin Gandhi, BPharm, PhD**, Health Economics and Value Assessment Business Partner, Sanofi, Cambridge, MA, USA

Economic evaluation of digital health interventions: methodological issues and recommendations for practice.

Gomes M, Murray E, Raftery J. *Pharmacoeconomics* 2022;40(4):367-378.

Summary

The article by Gomes et al provides a detailed understanding of the characteristics of digital interventions and its impact on methodological considerations for economic evaluation. Compared to standard technologies or medical interventions, the economic evaluation of digital technologies may require differing design considerations, choice of comparators, study perspectives, and methods for measuring model input parameters. Further, approaches for reporting the results of the analysis would also differ based on the approach adopted for the economic analysis of the digital intervention. Overall, the article provides key guidance to further grow and advance the understanding of methodologies for economic analysis of digital interventions.

Relevance

Compared to standard therapeutic interventions, the challenges associated with the economic evaluation of digital interventions are varied and still not well understood across the healthcare domain. A primary reason for this is the nature of digital interventions such as the need for user input on a constant basis, differential pricing, and rapid and dynamic evolution cycles compared to standard technologies. While still at its nascent stages, there is a need for focused development of standardized methodologies for the economic evaluation of digital interventions given their fast-growing relevance and importance for disease management and control.

Digital interventions in mental health: evidence syntheses and economic modelling.

Gega L, Jankovic D, Saramago P, et al. *Health Technol Assess*. 2022;26(1):1-182.

Summary

This study by Gega et al uses a 4-step approach to evaluate the value of digital interventions for the management of mental health conditions. First, the authors identify and summarize sources of published economic evidence on digital health interventions for mental health conditions. Second, they synthesize clinical evidence associated with a single mental health condition (generalized anxiety disorder) to be used for constructing an economic model. Third, they build an economic model based on the collected economic and clinical evidence on generalized anxiety disorder. Fourth, the authors engaged with stakeholders to identify how they evaluate and perceive the value of digital interventions. The authors found that while digital interventions are cost-effective compared to nontherapeutic controls, their value in comparison to pharmacological therapy remains unclear. The economic model for general anxiety disorder showed that digital health interventions were associated with a lower net monetary benefit compared to medication therapy. In their interaction with stakeholders, the authors identified reduced wait times to receive care, ability to provide access to underserved populations, and maintaining continuous care as critical motivators for the adoption of digital interventions.

Relevance

The authors highlight the need to develop digital interventions than are not only less costly but also more effective than available alternatives for effective management of underlying disease conditions.

A framework for the economic evaluation of digital health interventions.

Wilkinson T, Wang M, Friedman J, Prestidge M. World Bank Group. Policy Research Working Paper 10407. Accessed March 24, 2024. https://documents1.worldbank.org/curated/en/099446504122313917/pdf/IDU0f639726d0f11404a3509af8054677649dcd6.pdf.

Summary

In this working paper, the authors describe a framework for determining the economic value of digital health technologies. The authors propose 5 key steps within their framework. First, the context or study perspective of the evaluation should be determined. Second, the appropriate evaluation type best suited to quantify the value of the underlying digital intervention should be selected. Third, the level of complexity associated with the evaluation approach should be determined. Fourth, the methodology associated with selected intervention should be determined. Fifth, the value proposition including uncertainties and impacts associated with the findings should be presented to decision makers.

Relevance

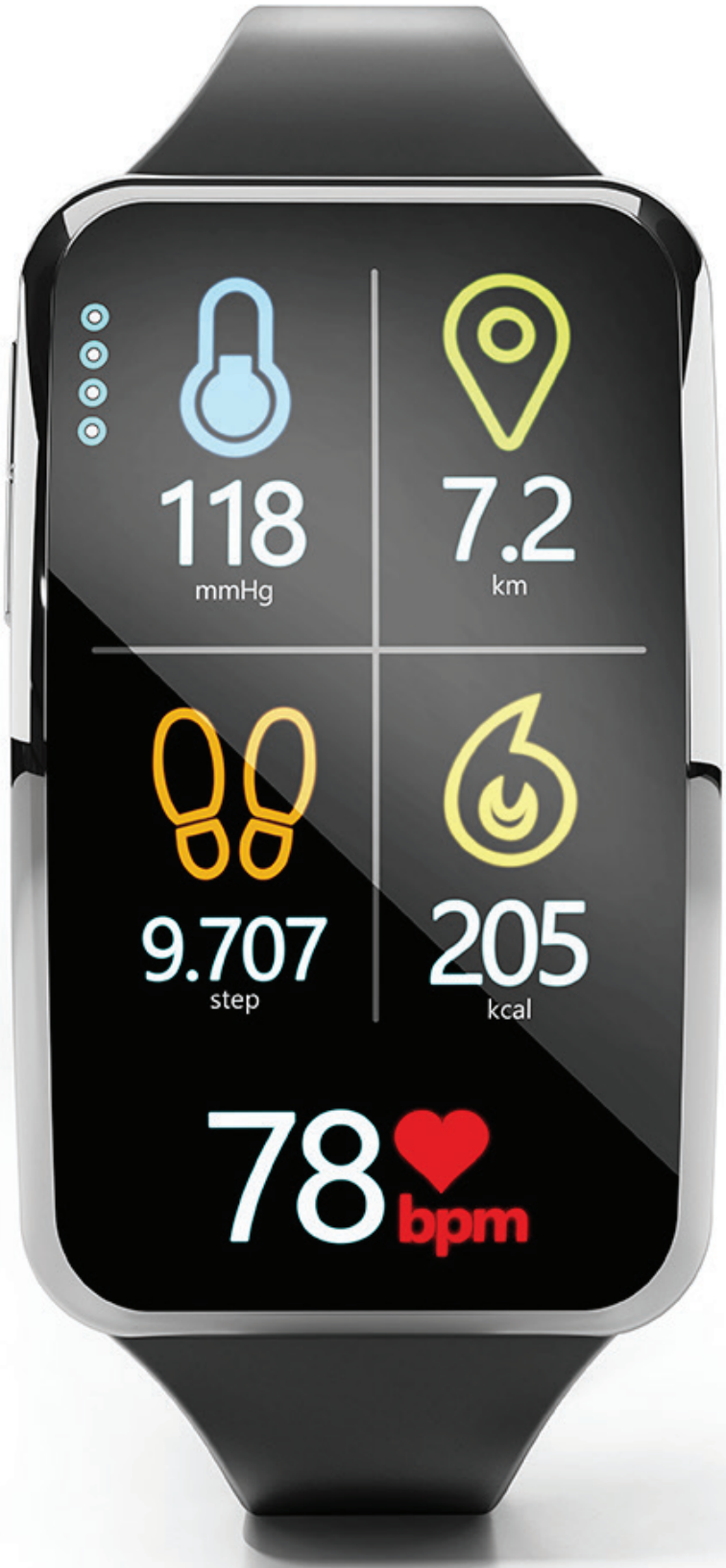
The proposed framework would help payers and policy makers understand the results of digital health economic evaluations in context of the transparently presented methodology to make informed decisions on reimbursement and approvals associated with digital health interventions, especially in low- to middle-income countries with constrained resources.

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.*

Defining Digital Health & Getting Clarity for HEOR

By Christiane Truelove

The phrase "digital health" encompasses a wide variety of things—telehealth, consumer wearables that track health data, the use of monitoring devices in clinical trials to generate hard data about clinical endpoints, and apps that are combined with a drug or medical device for treatment or can actually act as the therapeutic themselves. From data and health information technology to healthcare delivery and interventions, it's easy to get lost in the maze of complexity posed by digital health.



HEALTH ECONOMICS AND OUTCOMES RESEARCH (HEOR) experts need the tools and terminology to be able to evaluate these new technologies. The problem is that the complexity surrounding digital health tools—including overly broad, vague terminology—makes it difficult to apply the same frameworks used to evaluate drugs and devices.

"Digitalization is basically cheaper information," explains Zsombor Zrubka, MD, PhD, associate professor of Óbuda University in Hungary and a member of ISPOR's Digital Health Special Interest Group. "Therefore, it's simply just more information. And what does it mean? It means that it can make healthcare cheaper; it can optimize existing treatments; it can bring in new treatment opportunities that were unavailable before; and it can make everything more accessible."

There are 2 ways that digital technologies are relevant for doing health economic research, according to Ariel Dora Stern, PhD, professor of digital health, economics, and policy at the Hasso Plattner Institute. Stern is also on the advisory board of the Peterson Health Technology Institute, which creates assessment frameworks for evaluating digital health technologies. "The first is that the digital technologies are themselves an intervention." For example, there are apps for chronic disease management and apps that can deliver cognitive behavioral therapy for someone with substance use disorder. "The other way digital technologies are relevant in health economic assessments is actually using those technologies to collect data or any patient-relevant measures that would be difficult to quantify or otherwise be extraordinarily cumbersome to collect when it may have a really meaningful impact on patient quality of life," Stern says.

> "It [digitalization] means that it can make healthcare cheaper; it can optimize existing treatments; it can bring in new treatment opportunities that were unavailable before; and it can make everything more accessible."
>
> – Zsombor Zrubka, MD, PhD

Stern cites an example of how useful digital technology can be in gathering difficult-to-track data. In a recent study, she and colleagues from University Hospital Dusseldorf and Brigham and Women's Hospital looked at the use of digital health technologies in neurology to measure such things as cognition, sleep tracking, and motion tracking. Stern says this is important because tracking sleep is key in evaluating the effect of many neurological diseases, and sensors can give hard data on sleep amounts or quality rather than relying on patients' own recollections. These sensors can also collect data in a more patient-centric way.

What to measure and how?

Stern notes there is already a framework for evaluating the tools used for data collection: the V3 framework—verification, analytical validation, and clinical validation to determine fit-for-purpose of biometric monitoring technologies. "Where it becomes interesting is when the digital technology is the intervention itself—because then we very quickly, for all sorts of reasons, slide into the mode of saying, "Well, we know how to do randomized controlled trials for healthcare products, and in many ways, this just looks like a new kind of therapeutic medical product."

"We do randomized controlled trials for new drugs, medical devices, or surgical procedures—we know how to do this. And the instinct is 100% correct, which is that in the spirit of evidence-based medicine, we want to have evidence that technologies work before you have clinicians recommending them for patients." And payers won't want to cover a product if there is no evidence that it does anything at all, she adds.

Developing and understanding the endpoints HEOR experts will need to evaluate digital health technologies—whether a standalone app to treat a condition, a digital diagnostic, or something to evaluate a drug or medical device—is important because "we say what we would like is an intervention to be used when it's effective, when it improves health, when it leads to better outcomes, when it increases efficiency, and when it gives patients personalization or the involvement in their own healthcare," says Anita Burrell, founder of Anita Burrell Consulting LLC and chair of ISPOR's Digital Health Special Interest Group. "That's the promise of digital health—this promise to have efficiency improved outcomes, personalization, patient involvement, the possibility to be able to monitor patients more effectively so that we get a better understanding of how medicines may or may not be working or how their conditions develop."

Standardizing digital health terms is important when it comes to the payers looking at whether they will fund digital health interventions, "their requirements for digital health have been far more diverse between different authorities granting reimbursement," Burrell says. The problem when it comes to HEOR evaluations of digital interventions, however, is "they have far more components than the technologies that we're used to evaluating," Burrell says.

In a randomized controlled trial with a patient either taking a drug or a placebo, it is a fairly simplistic intervention. In a trial evaluating a drug, the class of the drug is known, even the subclass, and often the specific biological system pathway it is supposed to affect is understood. Within what Zrubka calls "the classical" HEOR fields, when it comes to pharmaceuticals, researchers know how to state their research questions: Who is the patient? What is the treatment? What is the comparator? What are the outcomes, etc. "By collecting this information, you can say, 'This is a better treatment than that,'" he says.

However, when looking at a digital health intervention, "we've had this explosion of digital technologies and everything comes under this big umbrella," Burrell says. Terms such as

digital health, eHealth, mHealth, or telehealth are not very well defined from each other, making these interventions much more difficult to evaluate.

"Are we able to conduct research to extract that evidence—to synthesize that evidence—with the same effort, efficiency, or effectiveness as we do with for drugs?" Zrubka asks. In analyzing more than 500 systematic reviews, he and Burrell found the terms *digital, mobile, telemedicine*, and *eHealth* have more than 100 definitions. "And we found that each year, 10 new definitions were created." Drilling down further yielded 67 more secondary terms including *telehealth, telestroke, telesurgery*, and *teledermatology*, he adds.

According to Zrubka, "If we do research this field, we need to communicate using clear terminology, and then we are able to help all the users because they can get the information that they need for the decisions."

How would digital health RCTs function?

Stern says while it would be difficult to do blinding in a randomized controlled trial of a digital therapeutic, there are ways a digital therapeutic trial would have advantages over a traditional drug or device trial. "You have a much richer set of data because digital products, by nature, come with a lot of metadata," she notes. Another way trials for digital therapeutics may have an advantage in evidence generation compared with those for conventional drugs or devices is in the tracking compliance. "Only the most diligent pharma trials will have adherence measures built in, and that's typically because they're for medicines where it's really important that a patient take that drug at the same time every day," Stern says. "It's very difficult to measure compliance, so we measure 'intent to treat,' which is different than 'Did the patient actually take the drug and then what is the effect?'"

While it's not always possible to track compliance with a digital therapeutic, it is far more likely that there will be "digital exhaust" that can be tracked, Stern says. "Let's just imagine this is some form of behavioral therapy that the patient is doing in an app-based way. If they're supposed to spend 14 minutes per day doing their cognitive behavioral therapy exercises, you can actually see if they had the app open and were engaging with it when things are time stamped." These kinds of data can create a number of new opportunities for studying these products, she adds.

"I'm a big supporter of practicing evidence-based medicine, but the strategies that we typically employ for evidence generation for new medical products are just not perfectly suited—and certainly not at all well-suited in the long-term—for studying digital products," Stern states. "And that's where we, as a research community, have to be honest with ourselves and then get creative about methods and not compromise our standards."

It's also important to set these standards for evaluating digital therapeutics to alleviate the frustrations of manufacturers, Burrell and Stern note.

"The requirements for digital health have been far more diverse between different authorities granting reimbursement," Burrell says. In the United States, a manufacturer may be able to obtain reimbursement from 1 state Medicaid system, but not another. "The funding is more piecemeal."

According to Stern, "There's this frustration that you hear from companies that are doing diligent work to study their products," Stern says. "They're running appropriately powered trials yet having a very difficult time differentiating themselves from the massive offerings out there, which include a number of products for which there simply isn't any high-quality evidence available."

"I'm a big supporter of practicing evidence-based medicine, but the strategies that we typically employ for evidence generation for new medical products are just not perfectly suited–and certainly not at all well-suited in the long-term–for studying digital products."

– Ariel Dora Stern, PhD

Establishing standards for determining the value of digital health products "certainly raises the bar, but in a way that will incentivize manufacturers and other organizations to do higher quality research and will stimulate good value-creating products because it will actually create a market for them," Stern says.

Digital health and ISPOR

Zrubka is the co-chair of ISPOR's Delphi Study on Defining Digital Health Interventions. He and Burrell have aimed to define digital health terms for HEOR in "How Useful Are Digital Health Terms in Outcomes Research?" This paper advocates that umbrella terms should be accompanied by medical subject headings terms reflecting population, intervention, comparator, outcome, timing, and setting (PICOTS). A functional classification system that creates standardized terminology for digital health interventions will allow researchers to focus evidence summaries for outcomes research. The new PICOTS-ComTeC framework is a flexible and versatile tool, intended to assist authors in designing and reporting primary studies and evidence syntheses, yielding actionable results for clinicians and other decision makers.

"Hopefully, the PICOTS-ComTec checklists that we've produced and the push to rationalize some of the requests from reimbursement authorities for digital health technologies will actually start to improve the efficiency, the outcomes, the personalization, and the patient involvement through digital health," Burrell says.

By the Numbers: Digital Health

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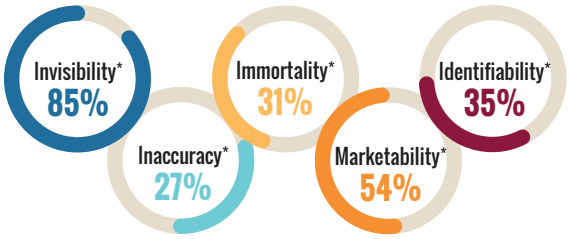
Data Privacy and Ownership of Digital Health Data

5 Key Challenges for Health Privacy of Digital Technologies

Invisibility: people unaware of how they are tracked
Inaccuracy: flawed data
Immortality: data never expire
Marketability: data are frequently bought and sold
Identifiability: individuals can be readily reidentified



**Percentages are derived from a survey of 26 participants*

Opportunities

Public and citizen engagement: conduct public awareness campaigns on data sharing benefits, risks, and success stories to build understanding and trust.

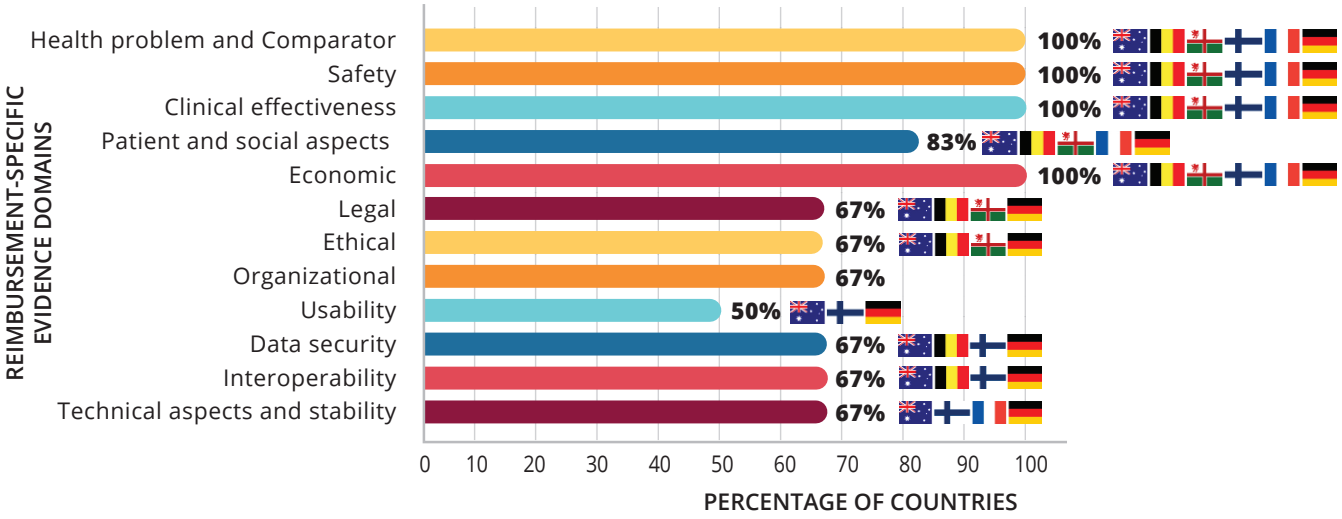
Clarity and transparency: establish shared goals, core principles, and regulatory processes for data transparency and terms of use.

New regulatory framework: advocate for a radical shift in data usage regulation by industry towards user control over data generation.

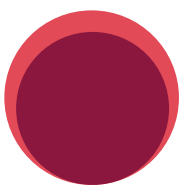
New data structures and Big Data analytics: develop clear interoperability standards, federal architectures for data storage, real-time analytics, and transparently regulated third-party data registries to facilitate safe data sharing while supporting interdisciplinary collaborations.

Training and education: equip citizens, healthcare professionals, and future workforces with essential skillsets to take advantage of the digital revolution.

Use of Digital Health Data for Funding and Reimbursement Decisions



Trends in Physician Adoption of Digital Health Technologies: Growth from 2016 to 2022



85% → 93%
Physicians who think digital health tools are an advantage for patient care

14% → 80%
Physicians using digital technologies to hold virtual visits with patients

12% → 30%
Physicians using remote monitoring devices (eg, apps to measure weight, blood pressure, blood glucose, etc)

Sticking With It: Assessing Adherence Rates in Real-World Studies Using Digital Technologies

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In order to draw robust, generalizable conclusions from real-world studies, participant adherence to data capture activities is vital.

A targeted review of real-world studies using digital technologies showed no overall trend to indicate that adherence was dependent on specific factors, including data collection frequency, study duration, or location.

This article explores several methods that could be utilized during the design and execution of real-world studies that can encourage adherence, such as patient cocreation and incentives.

Introduction

Longitudinal observational studies play a central role in advancing understanding of the onset and progression of physical and mental health conditions in the real world[1] and help with extrapolating data obtained in randomized controlled trials.[2] Once recruited, participants in longitudinal studies are asked to adhere to data capture activities at specified timepoints. Leaders of pharmaceutical and biotech organizations have identified patient recruitment—including participant retention—as the main challenge in real-world evidence generation.[3] Ensuring participant adherence or engagement in these studies is important to avoid attrition (ie, participants leaving the study or being lost to follow-up) and poor completion (ie, remaining in the study but not providing complete data). Poor adherence can reduce the generalizability of outcomes and the statistical power to detect effects of interest.

As the use of digital technologies increases, researchers are able to gather data from patients using online surveys and questionnaires accessible through mobile phones and computers. However, some data show that such digital studies can be affected by poor participant adherence.[4] Adherence is particularly important for data capture activities using digital technologies that are completed without the supervision of clinical staff at physical study sites.

This article assesses participant adherence rates in real-world studies, with a focus on those using digital technologies.

Adherence in real-world studies using digital technologies

The adherence rates to data capture activities that are reported in the literature vary considerably. A targeted review of publications involving real-world studies using digital technologies from the last 10 years on PubMed and Google Scholar yielded 14 relevant results.[5]

Among the 9 studies with daily data collection, adherence to data capture activities ranged from 9% to 96%. Two studies implemented weekly data collection, with adherence ranging from 63% to 84%. Among the 3 studies with the least frequent data collection, adherence by the end of the study ranged from 1% to 38%. The total data collection period of all studies varied; the studies with the most frequent data collection (daily) had the shortest total data collection period, ranging from 7 to 141 days. However, the studies with the least frequent data collection (ranging from once per 3 months to yearly) had the longest total data collection period, ranging from 1 to 4.5 years. A full breakdown of the types of study participants, the locations, and key findings can be found in **Table 1**.[5] Overall, no trend was observed to indicate that adherence was dependent on specific factors, including data collection frequency, study duration, or location. The number of studies reviewed in this article might not have been large enough to draw robust conclusions. A systematic review or meta-analysis may help to further explore whether specific study characteristics impact adherence rates.

> Leaders of pharmaceutical and biotech organizations have identified patient recruitment–including participant retention–as the main challenge in real-world evidence generation.

Potential strategies to improve adherence

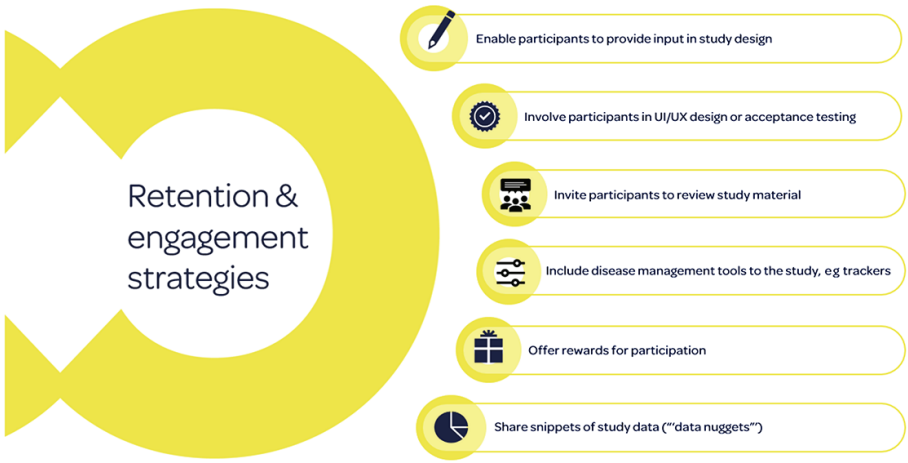
Including participants in the development process may increase the likelihood that they will have greater engagement once the study launches. Participants can be involved in the development of real-world studies by providing input in study design or reviewing participant-facing material,[7-9] contributing to UI/UX design or acceptance testing.[10-15]

Table 1: Overview of adherence rates in real-world studies using digital technologies[5]

Author(s)	Study participants	Study location	Data collection period	Data collection frequency	Key finding(s) on adherence to data collection activities
Artinian, et al (2003)	Patients with congestive heart failure	USA	3 months	Daily	85% of participants completed daily weight monitoring and 81% of participants completed blood pressure monitoring activities
Cormack, et al (2019)	Patients with mild-to-moderate depression	UK	6 weeks	Daily	A mean 96% of participants completed the daily cognitive assessment across the 6-week period
Di Fraia, et al (2020)	Patients with seasonal allergic rhinitis	Italy	7 weeks	Daily	Mean adherence during the final phase of the study (approximately day 47+) was 79%
McConnell, et al (2017)	Members of the general public	USA	7 days	Daily	9% of participants completed all 7 days of data collection
Paramore, et al (2021)	Patients with transfusion-dependent beta-thalassemia and caregivers	Italy UK USA	90 days	Daily	45% of participants responded to the daily patient-reported outcome instruments
Rudell, et al (2016)	Patients with multiple sclerosis and clinicians using the app to interact with patients	USA	Not defined	Daily	31% of participants in the study used the app daily
Weerts, et al (2020)	Patients with irritable bowel syndrome	The Netherlands	70 days	Daily	88% mean completion rate of the daily digital symptom diary during all 70 days of study duration
Weisel, et al (2014)	Patients with asthma	USA	27–141 days	Daily	52% of participants completed the daily questionnaire on 90%+ of their time in the study 72% of participants completed the daily questionnaire on 80%+ of their time in the study 100% exceeded 50% of the eligible days
Xu, et al (2018)	Members of the general public	USA	4 weeks	Daily	68% of participants completed all 28 questionnaires
Amorim, et al (2021)	Emergency department patients with lower back pain	Australia	4 weeks	Weekly (weeks 1, 2, and 4)	Out of 51.5% of participants who completed the week 1 survey, 84% completed the final week 4 survey
Barber, et al (2016)	18- and 19-year-old women from the general public	USA	2.5 years	Weekly	Adherence to completing the weekly survey at 2.5 years was 63%
Pathiravasan, et al (2021)	Members of the general public	USA	1 year	Every 3 months	Only 1% of participants completed data capture activities 12 months into the study
Lee, et al (2018)	Patients with myasthenia gravis	USA	4.5 years	Biannual survey	21% response rate for the ninth follow-up biannual survey on prednisone steroid use
Loxton, et al (2019)	Young women born between 1989 and 1995	Australia	3 years	Yearly	All 3 follow-up surveys were completed by 38.21% of women

Additional strategies can be implemented during the study, particularly for real-world research using digital technologies, as summarized in the **figure**.[6] Disease management tools such as trackers can be implemented to improve completion rates,[16] and offering rewards for participation can improve engagement.[17,18] Of the studies reviewed in the literature review, 6 reported offering participants incentives for completion of data capture activities.[5] None, however, explored whether incentives impacted adherence to data capture activities.[5] Finally, participants could also be sent regular "data nuggets"

Figure. Retention and engagement strategies.



with snippets of study data to encourage continued adherence.[19]

Conclusion

Real-world research is crucial when creating a broad and granular picture of a disease or research area.[2] In order to draw robust, generalizable conclusions from real-world studies, participant adherence to data capture activities is vital. Several methods could be utilized during the design and execution of real-world studies that can encourage adherence, such as patient cocreation and incentives.

> In order to draw robust, generalizable conclusions from real-world studies, participant adherence to data capture activities is vital.

Future research could also focus on a detailed investigation of the relationship between incentives and adherence to data capture activities, as well as other means of patient involvement in the study design. It is important to understand the factors that may affect adherence, in order to inform the design of future studies.

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Digital Diagnosis Validation in Patient-Centered Research

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Diagnosis validation is a key component of the recruitment process, allowing researchers to certify a participant's eligibility to enroll in studies based on their diagnosis, while simultaneously informing the validation of other inclusion criteria.

A multitude of diagnosis validation features have been developed and integrated into digital patient-reported studies over the years–patient attitudes towards these features, however, remain to be explored.

This article sheds light on this topic by delving into the findings of a study that surveyed patient perceptions of a digital diagnosis validation feature, including its perceived ease of use and overall convenience.

Introduction

In today's medical landscape, digital patient-reported real-world studies have emerged as pivotal contributors to assessing treatment value and effectiveness in clinical practice. Within these studies, diagnosis validation serves as a critical component of the recruitment process, ensuring participant eligibility and data reliability. A multitude of diagnosis validation features have been developed and integrated into digital patient-reported studies over the years—patient attitudes towards these features, however, remain to be explored.

This article sheds light on this topic by delving into the findings of a study that surveyed patient perceptions of a digital diagnosis validation feature, including its perceived ease of use and overall convenience.

The Importance of Diagnostic Validation

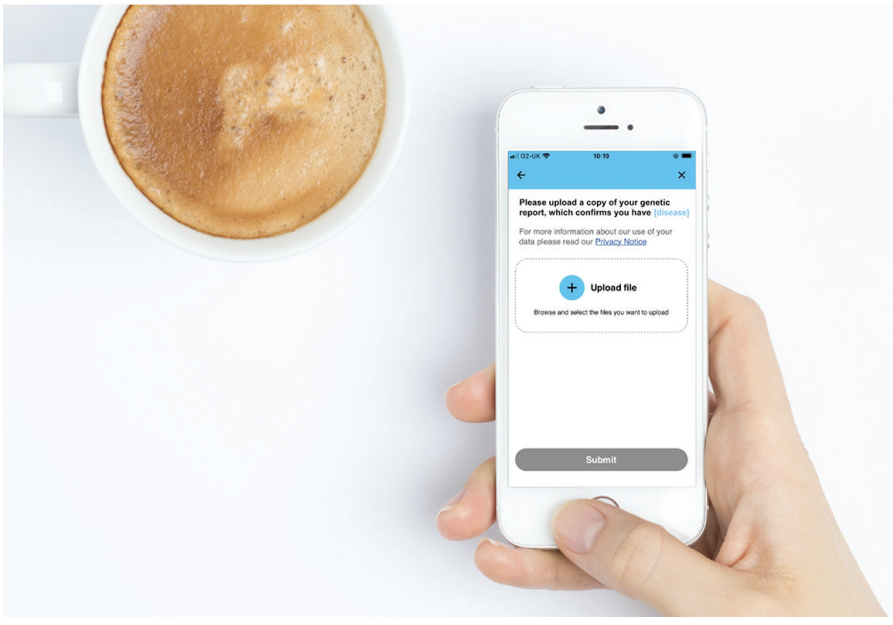
Diagnosis validation is a key component of the recruitment process, allowing researchers to certify a participant's eligibility to enroll in studies based on their diagnosis, while simultaneously informing the validation of other inclusion criteria (eg, confirmation of a condition-specific prescription can function as a form of diagnosis validation and fulfillment of an inclusion criterion).

The diagnosis validation process is of particular importance when the target population is hard to reach, as is often the case when proposing studies including participants with rare diseases that collect real-world evidence.[1] The recruitment and diagnosis validation process must therefore be carefully planned to maximize recruitment, while also ensuring that the diagnoses provided to investigators are genuine and accurate. One innovative method asks prospective participants to digitally submit a diagnosis letter or proof of medication packaging during the enrollment stage.

Patient Perspectives: Unveiling Attitudes Towards Digital Diagnosis Validation

A web-based survey completed by 22 individuals aged between 28-74 years with various chronic medical conditions yielded insights into the prevailing attitudes towards the use of a digital diagnosis validation feature (**Figure 1**). Over half of respondents indicated that obtaining proof of their medical diagnosis would be straightforward, whereas

Figure 1. An example diagnosis validation feature shared with respondents.

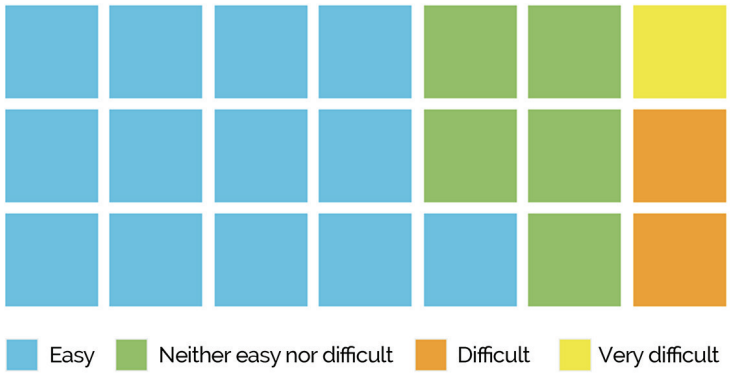


over one-third anticipated challenges, primarily due to poor cooperation from healthcare facilities. Of the former group, the largest proportion already had proof of diagnosis, whereas of the latter group, three-quarters did not.

> Utilizing a digital diagnosis validation feature–where participants are required to upload proof of their diagnosis–can be effectively implemented in different patient populations.

When asked about their preferred format for retaining proof of diagnosis, half favored hard copies, while one-third preferred digital copies. The majority expressed comfort in sharing proof of their medical diagnosis as part of study enrolment, and the largest proportion regarded the use of an upload feature to be easy to navigate (**Figure 2**).

Figure 2: Responses to "How would you find it to use the upload feature?" (n=21)



Shaping The Future Of Digital Real-world Studies

Findings suggest that utilizing a digital diagnosis validation feature—where participants are required to upload proof of their diagnosis—can be effectively implemented in different patient populations. Moreover, the positive feedback on the use of the upload feature indicates that participants would find the process straightforward and user-friendly, which is vital for ensuring high engagement and participation rates in digital real-world studies.

Similarly, the study revealed a generally positive attitude towards sharing medical information as part of the study enrollment process, emphasizing the potential for successful recruitment and data collection.

> As studies continue to take advantage of the remote data collection capabilities of smart devices, digital self-diagnosis validation will play an increasingly central role in the recruitment process.

By incorporating these digital features, researchers can establish a reliable alternative to traditional clinical site-based recruitment for digital real-world studies. This approach can enhance the convenience and accessibility of participation, which can potentially increase the diversity and representativeness of study samples.

Concluding Remarks

Moving forward, as studies continue to take advantage of the remote data collection capabilities of smart devices, digital self-diagnosis validation will play an increasingly central role in the recruitment process. Therefore, with time, it is hoped that evidence-based literature is built to interrogate and support the reliability of digital diagnosis validation. This normalization will in turn help diagnosis validation to be viewed as the beginning of a conversation between the participant and investigator, encouraging a collaborative approach to maximize the success, efficiency, and accuracy of prospective studies.

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The Synergy of Real-World Evidence and Digital Health Tools for Patient-Centric Outcomes

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The key to health economics and outcomes research in the modern healthcare landscape is harnessing real-world evidence from sources like electronic health records, wearable tech, and digital health apps to enhance health outcomes and cost-efficiency.

Patient-centricity has always been essential to healthcare innovation, but is becoming a bigger part of the conversation, especially as digital tools bridge gaps in access and understanding.

Despite the promise of digital health, there are limitations, including data privacy concerns, technological literacy, and access in underserved areas.

As patient centricity takes center stage in healthcare, the fusion of innovative digital health tools with real-world evidence (RWE) is revolutionizing how we understand and optimize patient outcomes, challenging age-old research and care delivery norms.

HEOR Overview

Health economics and outcomes research (HEOR) is vital for developing cost-effective and health-optimizing policies. Innovation in healthcare, whether through clinical studies or postmarket research, is an extensive and costly process. To maximize health outcomes and cost-efficiency, real-world evidence (RWE) has become a major focus of HEOR. RWE involves real-world data gathered from sources like electronic health records (EHR), mobile apps, claims data, and patient registries.[1]

The use of RWE marks a paradigm shift in HEOR, as it has the potential to reduce research costs and provide accurate clinical surveillance. Digital health tools such as mobile apps, wearable devices, and software are transforming the healthcare landscape, providing robust data sets from user activity. This provides a unique opportunity for emphasizing patient-centricity. In this article, we aim to explore the intersection of patient centricity in RWE with the use of digital health tools.

> The use of real-world evidence marks a paradigm shift in HEOR, as it has the potential to reduce research costs and provide accurate clinical surveillance.

Patient-Centric Care

Patient centricity involves engaging patients in healthcare innovation and processes.[2] The value of pharmaceutical development and health interventions is reflected in the patient outcomes produced. Patient goals and principles should be a primary focus of healthcare providers and organizations. Patient-centered care empowers patients in their health decisions, fosters accountability, and focuses on patient priorities.[3] As conflicting health information becomes widely available, establishing provider-patient trust is a vital aspect of patient care and treatment adherence.

> Over 90% of physicians believe these digital health tools are beneficial for patient care and can even reduce physician burnout.

One method of improving patient centricity in healthcare is through the utilization of RWE. Exploring the real-world outcomes of a drug or intervention can benefit every stakeholder in the healthcare ecosystem—from patients and caregivers to providers, healthcare systems, industry, and everyone in between. For example, clinical data of drug efficacy and safety can fill in the gaps within randomized controlled trials (RCTs). As Blonde et al[4] highlights, the rigid structure of research settings and exclusion criteria can limit the generalizability of safety and efficacy outcomes. RWE can reveal the outcomes of an intervention from diverse, real-world medical practice without the cost and time required for RCTs.

The Rise of Digital Health Tools

Digital health tools such as mobile apps, wearable biosensors, and EHRs are becoming common practice for health-tracking and surveillance. Over 90% of physicians believe these digital health tools are beneficial for patient care and can even reduce physician burnout.[5] Globally, mobile apps aimed at smoking cessation, fitness tracking, symptom monitoring, and nutrition counseling are becoming widely accessible. Real-time monitoring of patient vitals, symptoms, and treatment plans can deliver valuable information about treatment fidelity and efficacy.

Many digital health wearables can be conveniently worn throughout the day and track data automatically. This has been especially useful for passive tracking of symptoms which would normally require extensive time. With these wearables, tracking an individual's blood sugar or heart rate has become as simple as checking their watch. In the era of digital health tools and telemedicine, RWE is becoming robust, accurate, and accessible.

The Synergy Between Patient-Centric Outcomes and Digital Health Tools

One of the main barriers to medical intervention or treatment adherence is access to care, especially in healthcare deserts. Digital health tools have the potential to bridge this gap and engage patients who would otherwise not have access. Collecting data from patients' daily life can provide improved insight into the true impact of drugs or medical devices. Utilizing a mobile app that can remind volunteers to check in regarding their symptoms or pain level is a unique method for real-time patient engagement. Assessing real-time patient outcomes is helpful for analyzing trends over time and identifying emerging effects of interventions. The data obtained through digital health tools are extremely accessible, as researchers can quickly view patient data through cloud-based software. Additionally, there is an opportunity for significant cost savings by using RWE, in stark contrast to the millions of dollars required for RCTs.

> Collecting data from patients' daily life can provide improved insight into the true impact of drugs or medical devices.

Outside of access, monitoring the outcome of health interventions on varied and diverse patient populations by using digital health tools is a pillar of patient-centered care. Patient care for diverse populations must include evaluating efficacy and safety of medications or devices for individuals of various occupations, geographic locations, and lifestyles.

Real-time data management is a useful tool to monitor patient conditions throughout clinical trials. For example, wearable devices that track heart rate and blood pressure changes can provide insight into the physiological changes in a way that is more objective than pain scales. Wearables utilized during sleep can provide valuable metrics to track medication and intervention effects outside of the lab. Mobile apps or wearable devices can also measure trends over time and the impact of certain patient environments, activities, and moods on various outcomes.

Challenges and Considerations

While digital-health tools can foster robust RWE, study researchers and participants will likely have concerns about their data privacy and security. When it comes to technology, especially artificial intelligence (AI)-based tech, garnering trust from the clinicians, payers, and even the general population can be difficult. Concerns surrounding privacy and consent are further escalated by the growing market of digital health, as social media platforms like Facebook may have access to users' personal health information. In February of this year, GoodRx, a telemedicine platform offering drug pricing information, discount programs, and online prescriptions, faced allegations from the Federal Trade Commission (FTC) for illegally selling health information to Facebook.[6] The FTC alleged that GoodRX patient data were used to target advertisements to users with certain health conditions based on their prescription history. Fitbit, a fitness-tracking wearable, also encountered recent controversy due to privacy concerns. The wearable company does not allow users to revoke consent for data sharing outside of the European Union (EU), breaching the EU General Data Privacy Regulation.[7]

The growing digital health market is ripe with opportunities for data breaches and patient privacy concerns. In a clinical trial setting, authentication concerns and data anonymization could be barriers to widespread use of this technology for research purposes. Policy makers and research stakeholders should carefully consider patient health data implications even in commercially available devices.

In the aging population, issues with technological literacy are a barrier to widespread use of health-related digital tech.[8] The aging population is increasing[8] and continues to face significant chronic disease burden. Digital health tools could be useful for improving healthcare access for individuals who lack transportation or need continuous care for chronic conditions. Certain wearables can be lifesaving in the event of a seizure, stroke, or fall.[8] However, a comprehensive understanding of health tech is crucial to accurate data collection and remote communication. Below-average technological literacy can make the use of wearables and other digital health tools less viable, especially in a research setting.

> The growing digital health market is ripe with opportunities for data breaches and patient privacy concerns.

According to research conducted by GoodRx, over 80% of counties in the United States are considered "medically underserved," which translates to an estimated 121 million people.[9] Digital health tools offer many opportunities to bring care to these populations in areas identified as healthcare deserts. However, the access limitations in these areas go beyond just healthcare to digital literacy and internet access. The successful implementation of digital health tools in healthcare deserts can be sustained only when there is corresponding expansion infrastructure, through initiatives such as community broadband networks and low-cost internet service options.[10]

Future Potential and Implications

Digital health technology will continue to evolve and integrate with most aspects of daily life. With the surge of mainstream AI-based software, at-home technology will become more accurate and capable. Long-term safety monitoring and symptom tracking can now be in the hands of patients through wearable devices and mobile surveillance reminders. Federal agencies, like the US Food and Drug Administration, are beginning to provide frameworks for the

use of RWE as a decision-making tool for new indications of previously approved drugs. Notably, several surveys of patients, including those in underserved communities, have indicated that patients are ready for digital health tools.

While the use of digital health tools can offer huge value, there are still gaps for those populations without widespread access to the internet and economic limitations. Technological literacy of the aging population, a group with a high burden of chronic illness, is also a barrier to certain uses of digital health tools for RWE. Innovators of this technology should evaluate the accessibility of their products and account for potential safety concerns regarding user data. As solutions are created to overcome these challenges, RWE will undoubtedly be a promising tool with the potential to monitor and improve health outcomes, especially in conjunction with the accessibility of digital health tools.

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Artificial Intelligence in HEOR

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The authors note the rising influence of artificial intelligence and its potential role in HEOR in the coming years.

The article stresses the importance of HEOR practitioners embracing continuous learning, and comprehending the suitability, risk, and limitations of the artificial intelligence tool for each use case.

The authors underscore the importance of integrating artificial intelligence into the overall business strategy and mention concrete use cases of artificial intelligence in HEOR as well as tools to make the impact tangible.

Artificial intelligence (AI) was the new buzzword at ISPOR's Europe Meeting 2023. While real-world evidence (RWE), the last big hype, still dominated the conference, with over 8 sessions, 1 short course on machine learning, and numerous posters on the topic, AI is rapidly catching up. The question is, what comes next for AI in health economics and outcomes research (HEOR)?

In this opinion article, we share our perspectives on what we think is a realistic potential trajectory of AI in HEOR in the coming years.

A particularly promising HEOR application of AI, and more specifically large language models (LLMs), is automating systematic literature reviews (SLR) and meta-analysis.[3] While there exist already several software solutions that facilitate AI-powered SLR tools, these use small machine learning models focused on the screening step—that is, they convert a publication's text into vectors (feature extraction) that are then used to rank publications on relevance (text classification). Simpler models include TF-IDF (weights words based on importance within documents) and Doc2Vec (creates vector representations for documents), used for feature

> A particularly promising HEOR application of AI, and more specifically large language models, is automating systematic literature reviews and meta-analysis.

extraction. These features can then be fed into classifiers like logistic regression or random forest for tasks like topic classification. In contrast, LLMs are more general-purpose models but much more expensive to train and run due to their size. Traditional models usually have up to thousands of parameters, whereas LLMs can have anywhere from hundreds of billions to trillions of parameters. We envision SLR software to increasingly integrate LLMs for purposes other than screening. One of these purposes will most likely be deriving the search strategy query from the PICO (Population, Intervention, Comparison, Outcome) and then translating it to the several available databases.

Another use is likely to be data extraction. LLMs can perform optical character recognition (OCR), a task that traditional models often struggle with due to their focus on structured data. This is crucial for handling publications in PDF format, where unstructured data, such as tables

> Another area where we see the potential of AI is in the development of economic models.

and complex formatting, are common. Another challenge in data extraction today is the varied presentation of similar information, such as different units or slightly different measurement methods for the same underlying concept. LLMs could address this by actively managing and ensuring uniformity in the extracted data, thereby significantly aiding the researcher's work. We also anticipate that SLR software will allow researchers to upload their own data extraction template. LLMs would then efficiently handle the task of populating this template, facilitating the developer to more easily make the extracted data in a downloadable format for other users. While we foresee LLMs will automate much of the process reducing work time, in our view human involvement in the loop will still be crucial, primarily focusing on quality control for verifying nuanced information and addressing potential biases and hallucinations. This collaborative approach, combining the efficiency of LLM automation with human expertise, could mitigate biases and enhance the overall quality and relevance of SLRs to ultimately ensure the job of the AI algorithm is as good as the one a human researcher could have performed.

Although this is an emerging field, early empirical research on data extraction for evidence synthesis using different LLMs shows promising results. While achieving human-level performance remains a challenge today[1,2] we foresee these early advancements to trigger amendments on SLRs guidelines to achieve greater transparency on the algorithms used.[3]

> The integration of large language models promises a substantial boost in productivity, emphasizing the need for professionals to embrace continuous learning to stay competitive in a rapidly evolving landscape.

Another area where we see the potential of AI is in the development of economic models. Traditionally, health economic models have been constructed using specialized commercial software or spreadsheet tools, such as TreeAge or Microsoft Excel, respectively. However, the limitations of these tools, particularly in handling complex analyses, have raised concerns about the credibility and relevance of the assessments. In contrast, several experts advocate for the use of modern programming languages to reduce errors inherent in spreadsheet models.[3,4,5] Although some see the adoption of modern programming languages in the HTA environment as pivotal, we argue that a barrier for many HEOR practitioners is their own programming knowledge. Thanks to LLMs, this barrier has now been lowered as they possess a remarkable ability to generate human-quality code in various programming languages including R and Python. We foresee AI pair programmers like Github Copilot to become widely adopted.[6] As of today, Github Copilot already offers an extension for most code editors in Python and is available as an opt-in integration with RStudio.[7] Alternatively, for the ones who prefer to continue building their models in Excel, since Github Inc (GitHub) is a subsidiary of Microsoft Corp, the company has also made Copilot available in Excel.[8] Needless to say, AI pair programmers can also help generate code outside of the context of health economic modeling such as preparing data to run a network meta-analysis, writing the code of the network metal-analysis itself or visualizing its results for a scientific publication and broader dissemination.

Amidst the somewhat sensationalistic yet valid concerns of AI displacing human jobs, we strongly believe HEOR professionals will not be replaced by AI. From our perspective, the real professional impact they are likely to experience lies in how they adapt their individual skillset to utilize these technologies. In our view, leveraging AI technologies is somewhat akin to the historical moment when spreadsheet software like Excel emerged as a digital tool that replicated and significantly enhanced the functionality of paper-based accounting systems, widening the gap of opportunities between tech-savvy individuals and those resistant to technological integration. While in the past lots of bookkeepers and accounting clerks were replaced by spreadsheet software, the number of jobs for accountants increased.[9] In a similar vein, the integration of LLMs promises, in our belief, a substantial boost in productivity, emphasizing the need for professionals to embrace continuous learning to stay competitive in a rapidly evolving landscape.

HEOR professionals should have a high-level understanding of how large language models (LLMs) work before they can be used correctly. A recent publication concluded that current AI tools like ChatGPT did not match the quality of standard targeted literature review methods.[10,11] According to the authors, ChatGPT failed to identify a great number of publications that should have been included in an SLR and, more worryingly, suggested others that did not exist. These results are flawed because the tool chosen is not fit for purpose: ChatGPT is not meant to replace a database like Embase. The reason ChatGPT can search some databases but not Embase is because these have enabled a free programmatic way of interaction named API (Application Programming Interface). In these cases, a large language model like ChatGPT can act as an agent and search specific databases by transforming the prompt of the user into a correctly formatted API query. Searching on Embase with AI is possible but researchers would have first required an API license with Elsevier. The message is that while it is important that HEOR practitioners embrace these new technologies, we all should be mindful to do the necessary background research, making efforts to understand which technologies are appropriate for their intended use. HEOR practitioners need to be aware of the risks of these new tools as well. A good example is Scite, an AI tool that helps researchers by showing how articles are cited, indicating if the citation supports or contradicts the claim.[12] As we envision such AI tools to keep gaining popularity in HEOR, it is worth pointing out its risks. Scite's metrics, like the total number of citations, can make already-cited papers in HEOR even more popular. This makes it increasingly challenging for new ideas to gain attention. This phenomenon is often referred to as the "echo chamber" effect and it is one of the main risks of AI recommendation algorithms on social media platforms, which tend to show users content similar to what they have previously engaged with or liked.

> While it is important that HEOR practitioners embrace these new technologies, we all should be mindful to do the necessary background research, making efforts to understand which technologies are appropriate for their intended use.

As a result, users may be exposed to a limited range of ideas, reinforcing their existing beliefs and preferences. This can contribute to the amplification of popular or already-circulated ideas, potentially overshadowing new or diverse information.

Our second point was the need for AI to be integrated into an overall strategy with a clear return on investment proposition. While a life sciences company could decide to develop their own AI-enabled SLR solution, venturing into the development of digital products

rather than discovering new medicines should be a very conscious choice. Developing software requires time, effort, and specific expertise. Deviations from the core business models should be a careful long-term investment as it may prove more efficient to purchase these technologies directly from software vendors.

While SLRs or writing programming code for cost-effectiveness models are definitely very interesting uses of AI, other straightforward uses of LLMs like writing assistance or translation deserve some attention as well. While the challenges of adapting a broader evidence package to an HTA local body go beyond translation, this is still an easily implementable efficiency gain of LLMs to help speed up submissions.

Because most companies are cautious about sharing their confidential data with the tech companies behind AI tools, involving the legal department early is crucial. The legal team can navigate the complex landscape of data privacy regulations, intellectual property concerns, and liability clauses within contracts. Ensuring contracts clearly define data ownership, usage rights, and liability protections for both parties is vital. Secondly, if work is partially externalized to a vendor, choosing the right vendor is equally important. Companies should scrutinize potential vendors' ability to offer robust data security guarantees. This includes secure data transfer protocols, reputable cloud storage solutions, and regular audits of their security practices.

Finally, while we believe that LLMs will soon become a productivity tool widely available and seamlessly integrated into web-based email services, word processors, and spreadsheets, they are unlikely to remain free. In the future, they may become available to paid customers only. The current development of LLMs has been largely supported by venture capital investments. The competing companies behind them are operating at a loss due to the substantial costs associated with training and running these models, which require massive amounts of data and computational resources.[13] Hence, the reason tools like ChatGPT offer a wide range of functionalities for free is that such companies are betting on the potential of LLMs to revolutionize a wide range of industries and are willing to take a long-term view of their investments. Consequently, users should expect and be prepared for LLMs and research tools leveraging LLMs like Litmaps or ResearchRabbit to become more expensive.[14,15]

In conclusion, the integration of AI and more specifically LLMs is likely to have many applications in the field of HEOR. LLMs promise significant advancements, particularly in automating tasks like systematic literature reviews and writing code for economic models. However, realizing this potential necessitates a nuanced approach. A thorough understanding of both AI's capabilities and limitations is essential if the benefits of these new technologies to deliver a more rapid and robust evidence base to inform better healthcare resource allocation decisions are to be realized. Practitioners of HEOR must make efforts to understand the underlying functionality of these new technologies, alongside careful consideration of data privacy and intellectual property concerns. Collaboration with legal professionals is crucial to ensure a responsible AI implementation strategy that should contribute to an organization's existing objectives. We would like to encourage HEOR professionals to embrace AI thoughtfully as the field evolves rapidly, and we believe it can unlock substantial benefits for their present work, ultimately contributing to enhanced healthcare outcomes.

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Conflicts of Interests

The authors declare no financial or personal relationships with the entities behind the mentioned proprietary AI tools. The choice of these tools is based on independent use and judgement with the purpose of making the discussion more tangible.

Value Assessment Frameworks and Health Preference Research in Digital Health Technologies

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This paper explores value assessment frameworks in digital health technologies, highlighting the need for legislative support and market acceptance. It emphasizes the role of health preference research in navigating the complexities of the valuation of digital health technologies.

Despite legislative efforts, such as Germany's Digital Health Care Act, integrating digital applications into healthcare has faced challenges, including low user engagement, app withdrawals, and financial issues for manufacturers.

The discussion on value-based pricing reveals inconsistencies in valuing digital health technologies. New assessment strategies for these technologies recommend moving beyond traditional models to include real-world evidence and stakeholder engagement, underlining the necessity for adaptive policies that evolve with technology.

Introduction

The emergence of digital health technologies (DHTs) has precipitated a profound transformation in the delivery of healthcare, presenting unprecedented opportunities for customizing patient treatment and optimizing health service workflows. This technological evolution extends beyond mere enhancements in care quality; it represents a paradigm shift in the nexus between healthcare delivery and policy formulation.

The realm of DHTs has seen impressive advancements across various medical fields, with diabetes management standing out as one of the prime examples of how connected ecosystems and innovative applications can significantly improve patient care.

> The emergence of digital health technologies has precipitated a profound transformation in the delivery of healthcare, presenting unprecedented opportunities for customizing patient treatment.

Continuous glucose monitoring (CGM) systems represent a leap forward, allowing patients to monitor their glucose levels in real time without the need for traditional finger-prick tests. Devices provide continuous, dynamic glucose data directly to the patient's smartphone app. These real-time data can also be shared with healthcare providers, enabling more responsive and personalized diabetes management strategies.

Insulin management apps are another pivotal development. Apps integrated in CGM systems and insulin pumps offer personalized dosing recommendations based on real-time glucose readings and other patient inputs. This not only helps in optimizing glycemic control but also reduces the risk of hypoglycemia and hyperglycemia by adjusting insulin doses more accurately than conventional methods. By leveraging data analytics and machine learning algorithms, these apps can predict glucose fluctuations and suggest adjustments preemptively.

Platforms that integrate CGM data with electronic health records (EHRs) enable healthcare providers to monitor their patients' glycemic control remotely, facilitating timely interventions without the need for in-person visits. Digital therapeutics platforms combine CGM data with behavioral health interventions to address the lifestyle and psychological aspects of diabetes management. Platforms offer personalized coaching, nutritional planning, and psychological support to help patients adopt healthier habits and cope with the challenges of managing diabetes.

These examples illustrate not just the potential of DHTs to transform diabetes care but also the broader implications for healthcare delivery, evaluation, and policy. They demonstrate how advancements in digital health can lead to more personalized, effective, and patient-centered approaches to managing chronic conditions. This paper endeavors to dissect the pivotal roles played by value assessment frameworks and health preference research amid this transformative wave. Through an analytical lens, it scrutinizes the legislative and market mechanisms that either advance or curtail the assimilation of DHTs into the healthcare system. The aim is to unravel the complexities of legal structures, market receptivity, and the intrinsic value DHTs confer upon the health sector, with a view to shedding light on the overarching implications for health policy and the delivery of patient-centered care.

The Future of DHTs

In 2020, a paper[1] with the bold title "Want to See the Future of Digital Health Tools? Look to Germany" was published in the *Harvard Business Review*, discussing the introduction and evaluation of digital health applications (DiGAs) in Germany. The authors assert that the introduction

of DiGAs is expected to significantly influence the integration of DHTs into healthcare practices and patients' daily routines. In late 2019, the German parliament passed the Digital Healthcare Act, aiming to catalyze the digital transformation of its healthcare system. This law marked a significant step for Germany, which historically lagged in digital health compared to its peers. A key provision of the Digital Healthcare Act is the formalization of DiGAs. DiGAs are intended to support the treatment or management of medical conditions and could be prescribed by healthcare professionals or by the health insurance company directly. Therefore, they are included in the basic benefit package in Germany. They are part of a broader trend toward incorporating digital technologies into healthcare to improve patient outcomes and provide more personalized care.

> The introduction of digital health apps is expected to significantly influence the integration of digital health technologies into healthcare practices and patients' daily routines.

The law introduced a fast-track process, managed by the Federal Institute for Drugs and Medical Devices, allowing DiGAs to swiftly enter the market. Following a streamlined review, an app can be included in a central registry and prescribed by physicians and psychotherapists, with reimbursement from health insurance providers covering approximately 90% of the population. To be listed and remain in the DiGA registry, apps must meet specific standards, including data protection, information security, interoperability, and preliminary data on benefits. Additionally, they must be CE-certified in one of the European Union's 2 lowest-risk classes. If an app demonstrates "positive care effects," it can be directly listed; otherwise, it must show evidence of benefits within 12 months of being added to the registry. German healthcare policy was aware of the challenge and, as a first step, opted for medical devices at the lowest risk level to learn from experience. It is particularly noteworthy that a considerable number of manufacturers withdrew their applications after the consultation meetings because the evidence was insufficient. The next step, medical devices with slightly higher risk levels, will also be included from 2024. Also, the range of services will be extended to digital nursing applications.

Germany's approach to digital health was viewed as a potential model for other healthcare systems seeking to embrace digital innovation. However, the initial optimism is gradually waning as the anticipated success among manufacturers is not materializing, and the challenges seem to overshadow the opportunities. The challenges faced by Germany in the adoption of DHTs, particularly around the aspects of withdrawals and bankruptcies of manufacturers, reflect a complex interplay of regulatory, market, and operational dynamics. DiGAs, initially approved and listed for reimbursement under the statutory health insurance system, are later removed from this list. For a DiGA to be included in the service catalogue, it must demonstrate a certain level of efficacy and safety. If the ongoing collection of evidence fails to support the initial claims of benefit, the application may be withdrawn. Some DiGAs may not achieve the anticipated level of user engagement or integration into clinical practice. This lack of adoption can undermine their financial viability and lead to withdrawal.

Developing and maintaining a DiGA that meets regulatory standards for safety, efficacy, and data security requires significant investment. Smaller companies or startups may struggle with the financial burden, particularly if they encounter delays in market acceptance or reimbursement. Navigating the regulatory landscape and achieving a spot in the health insurance catalogue is a complex and time-consuming process. Even after overcoming these hurdles, manufacturers may face challenges in market penetration and user adoption. The reimbursement rates set by health insurance may not cover the costs of development, marketing, and maintenance, especially for DiGAs that require continuous updates and support.

The experiences in Germany underline the importance of creating a supportive ecosystem for DHTs that balances innovation with patient safety and efficacy. In the German healthcare landscape, the inception of DiGAs has served as a catalyst, spurring a comprehensive discourse on the integration of technological innovation within health policy frameworks.

Developments in Value-Based Pricing

The discourse surrounding DHTs necessitates a robust understanding of the international discussion of value-based pricing. This investigation underscores the potential of value-based pricing to recalibrate the economic landscape of health technology prices. Despite its promise, the sector grapples with a discernible lack of uniformity in determining the precise value attributes and pricing methodologies appropriate for the evaluation of DHTs. Global efforts, specifically the initiatives of the ISPOR Special Task Force, alongside frameworks developed by leading entities such as American Society of Clinical Oncology, European Society for Medical Oncology, National Comprehensive Cancer Network, and Memorial Sloan Kettering Cancer Center, were implemented to integrate an extensive array of value determinants into healthcare evaluation.

> This investigation underscores the potential of value-based pricing to recalibrate the economic landscape of health technology prices.

The initial enthusiasm for introducing DHTs in Germany, driven by the Digital Healthcare Act, appears to have encountered challenges dampening initial expectations. Manufacturers, healthcare providers, and regulatory authorities face several difficulties:

Low user numbers and the absence of anticipated success suggest lower acceptance and demand for DiGAs than expected, possibly due to lack of user awareness, insufficient integration into existing reimbursement of healthcare providers, or challenges in demonstrating clinical benefits.

- Removal of DiGAs from health insurance catalogs may indicate failure to meet effectiveness and safety criteria or insufficient proof of benefits, reflecting flaws in the evaluation process or manufacturers' difficulties in meeting required evaluation standards.

- Financial challenges and insolvencies among manufacturers may point to a tough market environment, high development costs, and regulatory hurdles.

- Given these challenges, revising the system for DiGA evaluation and integration might be needed to ensure its effectiveness in promoting innovative solutions while protecting patients and ensuring care quality.

This sheds light on the inherent challenges of implementing value-based pricing. An array of methodologies is deployed for quantifying a broad spectrum of value elements. The discourse dissects various value components utilized in value assessment frameworks, encompassing quantifiable measures like quality-adjusted life years, clinical outcomes, and productivity losses, as well as the more nuanced qualitative factors such as the value of hope and the real-option value. A critical examination of these valuation approaches ensues, considering their application across diverse disease areas and technologies, and assessing their potential for broader implementation in value-based pricing strategies.

New Assessment Approaches for DHTs

In the realm of DHTs, there's a clear distinction between innovative new products from emerging companies, like symptom checkers and the digitalization of existing processes by established players. The former are often disruptive, while the latter tend to be more incremental.

The rise of DHTs calls for a significant shift in how we evaluate their worth, moving beyond traditional methods to new frameworks that better capture their unique value. Research by Haig et al[2] and Main et al[3] emphasizes the need for a combined approach of regulatory vision and value-based assessment, aligning with the dynamic nature of DHTs. This research highlights the urgency of evolving regulations at the same pace as DHTs.

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This shift involves quickly adapting policies and balancing technological progress with patient safety. It requires engaging multiple stakeholders and integrating real-world evidence, which is crucial for understanding treatment effects from various sources, as noted by Kolasa and others[4,5] in 2023. With the growing role of individuals in decision making, it's also essential to include behavioral data in our assessments.

Challenges in the Valuation of DHTs

Even if there are currently few reliable figures, it is assumed that there are currently several hundred thousand DiGAs and that tens of thousands are added every year. A few of these have both a relevant and proven medical benefit and should therefore undoubtedly be part of the basic benefit package of a healthcare system.

The evaluation of DHT faces unique challenges due to its diverse range of products:

- DHTs are often part of complex interventions with effects that cannot be isolated.

- The value of DHTs often depends on multiple decision criteria, differently valued depending on the perspective (eg, clinician, patient, or payer).

- Technologies, rapid development demands swift market access.

- DHTs continually evolve, necessitating an adaptive evaluation model.

- Often developed by entities with limited resources, DHTs' sustainability and long-term impact can be uncertain.

The central challenge is therefore to develop an evaluation grid that assists quick and accurate decision making. There are fundamental decisions with DHT that should be addressed by a value assessment framework: (1) market access, (2) reimbursement, and (3) pricing.

Pricing is a particularly difficult topic and depends largely on the positioning of the DHT. Three basic logics are conceivable:

- DHTs substitute "status quo" therapies and accordingly there are few arguments why these existing therapies should not be a comparator for pricing decisions (eg, digital physiotherapy versus analog physiotherapy).

- DHTs bridge the gap until existing therapies can begin or may no longer be necessary. This is often the case with psychotherapy, where waiting times are often very long.

- DHTs complement existing therapies and should therefore be seen as an add-on. These include, for example, therapy support for oncological diseases or tinnitus.

The benefits of all 3 variants are unquestionable if the relevant studies are available but lead to fundamentally different approaches to pricing.

Strategic Recommendations

DHTs hold immense promise for transforming healthcare delivery, enhancing patient outcomes, and optimizing healthcare workflows. Their potential lies in enabling personalized medicine, improving chronic disease management (as seen in diabetes care), and facilitating remote patient monitoring. These technologies can lead to significant advancements in preventive healthcare, early disease detection, and patient engagement by providing digital tools that empower patients and healthcare providers with real-time data and analytics.

The challenges in DHT adoption often stem from issues related to reimbursement and market acceptance. Payers are crucial stakeholders in the healthcare ecosystem, and their caution towards new technologies can hinder

DHT adoption. Challenges include proving the cost-effectiveness of DHTs, navigating diverse reimbursement policies, and demonstrating clear clinical benefits to justify their inclusion in healthcare plans.

Patient perception of and demand for DHTs are pivotal for their successful integration into healthcare systems. While there's a growing interest among patients in technologies that offer convenience, better access to information, and personalized care, challenges remain in terms of usability, accessibility, and trust in digital solutions. Patient hesitance may arise from concerns over data privacy, the digital divide, or skepticism about the efficacy of digital interventions compared to traditional care methods.

While there's a growing interest among patients in technologies that offer convenience, better access to information, and personalized care, challenges remain in terms of usability, accessibility, and trust in digital solutions.

Examining other markets that have successfully adopted DHTs and established regulatory frameworks for their assessment can provide valuable insights. Countries like the United States, with the US Food and Drug Administration's Digital Health Innovation Action Plan, or the United Kingdom's NHS Digital, showcase how supportive regulatory environments can foster innovation while ensuring patient safety and efficacy of digital health solutions. The ongoing discussion highlights the importance of clear regulatory pathways, stakeholder engagement, and evidence-based standards for technology validation and market access.

In addressing the valuation of DHTs, it is essential to develop adaptive and innovative policies that match the emergent nature of these technologies. These policies should not only respond to current demands but also anticipate the future trajectory of DHTs, ensuring they are inclusive and resonate with the multidimensional aspects of digital health. The valuation complexity of DHTs arises from their inherent heterogeneity and the diverse impacts they have across the healthcare spectrum. Central to bridging the gaps in traditional assessment methods are real-world evidence and multiple criteria decision analysis. These methodologies enable a more nuanced and holistic appraisal of DHTs, capturing a range of benefits and risks not fully represented in conventional models. Moreover, health preference research is crucial in elucidating the value judgments of various stakeholders, providing structured insights into needs, preferences, and expectations.

A human-centric approach is imperative in the valuation of DHTs, addressing the unique spectrum of risks and benefits they present. Traditional methodologies often fall short in quantifying innovation and may not adequately capture the nuanced benefits of these technologies. This analysis must extend to the varied effects of DHTs on healthcare infrastructure, advocating for an approach that is both flexible and centered on patient needs.

Ultimately, the discussion underscores the need to forge new evidentiary benchmarks reflecting the evolving and dynamic lifecycle of DHTs. These benchmarks would facilitate the appraisal of current technologies and anticipate future innovations, ensuring a comprehensive and future-ready approach to valuing digital health technologies.

In support of the ongoing developments discussed, *Value in Health* announced a themed section, "Digital Health Technologies: Examining Value, Regulation, and Equity." This issue aims to address the complex interplay between technological innovation, health economics, and policy within the rapidly evolving domain of digital health technologies.

We invite submissions that explore the changing paradigms of digital health valuation and contribute insights for the future of healthcare technology assessment and policy. Researchers and practitioners are encouraged to submit manuscripts through the journal's online submission system by **September 1, 2024**, indicating in the cover letter that the submission is for the Digital Health Technologies theme.

This themed issue offers an opportunity to impact the discourse on the valuation, regulation, and equitable integration of digital health technologies into healthcare. We anticipate your contributions to shaping a more informed and effective approach to healthcare technology assessment and policy making.

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Q&A

Interview With Niklas Hedberg: Chair of the Executive Board, EUnetHTA

PharmaBoardroom caught up with Niklas Hedberg at DIA Europe 2024 in Brussels to gauge what more needs to be done ahead of the implementation of European HTA regulation in January 2025. Hedberg, who spoke at a host of panels across the event, also gave his take on the EU Pharma Legislation, the EMA's orphan drug designation, and general stakeholder awareness and understanding of the HTA/payer perspective.

"Our impression is that the HTA legislation ultimately looks for a better evidence base for HTA decisions. However, we should be mindful that the pushes for accelerated approvals and conditional approvals in the pharma legislation do not necessarily support this move towards a better evidence base."

– Niklas Hedberg

PharmaBoardroom: When we spoke around this time last year, you highlighted the big challenge for all stakeholders ahead of the implementation of European HTA regulation in January 2025. Nine months out, are all the ducks in a row? What is left to be done for the coordination group, national regulators, pharma companies, etc?
Niklas Hedberg: Yes, the ducks are in a row! Very clearly, there are now a number of formal documents that need to be finalized; basically, the 6 implementing acts. The first one was very recently published for a 4-week review period and 5 more are lined up.

We all realize that we are working to tight deadlines, and the Commission is the one responsible for the implementing acts. From a member state perspective, there are now two groups in the game: the HTAR coordination group and a comitology group, through which the secondary legislation runs.

On the coordination group side, there are 4 subgroups that are working very hard to produce the methodological and practical guidelines for joint clinical assessments and joint scientific consultations. A number of those will also come out quite soon.

I realize that there is an appetite to see what we have actually been doing up to this point, but we are now close to revealing this.

PB: To what extent is participation in events like DIA Europe an important part of sharing news and speaking to stakeholders outside of the HTA/payer bubble?
NH: We need to engage more, explain the system, and clarify the steps that we are taking. While no individual can give overarching statements on what, for example, the coordination group as a whole thinks, engagement and discussion is nevertheless crucial. The HTA Townhall at this conference, bringing together a panel from HTA bodies, the European Commission, patient groups, and industry, is a good example of this.

PB: Yesterday you talked about how every little piece of ink in the EU Pharma Legislation expands by the time it reaches downstream stakeholders like TLV (the Swedish Dental and Pharmaceutical Benefits Agency). Can you run us through some of your key concerns, and some of the ways that the Pharma Package contradicts or butts up against the HTA regulation?
NH: From the perspective of the European HTA Heads of Agencies Group (HAG), there is a clear recognition of the importance of this legislation. In a couple of areas—including defining unmet medical needs and evidence generation—we need to be mindful that the

methodology currently being worked out by the coordination group and referred to in the pharma legislation will eventually come close to the HTA legislation. HAG also recognizes the importance of being mindful of timelines; everything relating to timelines of regulatory processes in the pharma legislation will potentially have an impact on the timelines in the HTA regulation. Finally, we need to recognize that we already have good cooperation on joint scientific consultation.

On the national side, TLV—the agency that I represent in Sweden—is partly in line with that. Looking at the 2 legislations, our impression is that the HTA legislation ultimately looks for a better evidence base for HTA decisions. However, we should be mindful that the pushes for accelerated approvals and conditional approvals in the pharma legislation do not necessarily support this move towards a better evidence base.

There is also the issue of exclusivity times, perhaps the most sensitive point for the industry. At TLV, we feel that a ceiling should be considered to maintain affordability, one of the 3 pillars of the Pharma Legislation along with access and availability. We do though, of course, recognize the need to maintain the conditions for innovation in Europe.

Thirdly, we would like to see a reconsideration of the orphan drug definition. We appreciate the need for the orphan drug system. But from a payer perspective, the groups are too big, so we would like a special system with something closer to "ultra-orphan."

> In a couple of areas—including defining unmet medical needs and evidence generation—we need to be mindful that the methodology currently being worked out by the coordination group and referred to in the pharma legislation will eventually come close to the HTA legislation.

Our last point is that we would like to see a reconsideration of proposal to introduce transferable exclusivity vouchers to encourage R&D investment in antimicrobial resistance. We consider these the least cost-effective incentive method for new antibiotics development out of 3 alternatives, as detailed in a recent report on our website. There is broad alignment with other Swedish agencies on this point, although whether we will be able to garner international alignment remains to be seen.

PB: You raised the idea that you cannot have 100% "flexibility" and 100% "predictability" in the Pharma Legislation. Is your hope that, for now, we lean more on the side of "flexibility" and build in "predictability" later?
NH: There are so many wishes and wills and demands now. My message is simply to be mindful that 100% predictability means no flexibility and that 100% flexibility means no predictability. They are two sides of the same coin, so we all need to be mindful of where we strike the balance.

PB: At the unmet medical need panel, you said that the PRIME designation was the most interesting thing the European Medicines Agency (EMA) has done in recent times. Can you explain briefly why?
NH: This is my personal view alone: I feel that PRIME, for only the second time ever after the orphan drug regulation, meant that the EMA had to put certain products before others. The whole regulatory system is built on the idea that there are no limits to approval numbers, but PRIME has led to a mindset shift at the EMA. Thinking about prioritization is a game changer and means that they have started to talk our language as payers.

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This is not to say that I embrace everything that comes with PRIME, which is quite controversial in some of the HTA circles in which I move. Nevertheless, the prioritization aspect is very important and I am sure that sooner or later it will bring the EMA's reasoning a little closer to that of HTA bodies.

PB: I got a sense of frustration from you towards legislators, industry, and regulators on some of the panels. Do you think that sober payers' arguments are better received today than they were 10 or 20 years ago? I am thinking specifically about your insistence of the lack of an infinite money pot and that paying more for game changing innovations might mean paying less for incremental innovations…
NH: I did not want to come out as frustrated but for sure I think we need to be clear that budgets are limited. I think there is a slow but increasing understanding from most parties. The pandemic response, for example, was a good case study of different health values being put up against each other. We had to think about the medical value of isolating and preventing death from infection versus the downsides of loneliness and mental health issues. Then, all of a sudden, we got the vaccines, but in a limited number and had to prioritize which members of society should receive them first. In Sweden, we focused on the elderly and people with the highest risk factors first, with the healthier and younger parts of the population having to wait. Most people found that fair, but it was a prioritization.

Slowly, we had an awakening. I do realize that it is still challenging for a company or a patient group when an agency like ours does not accept a general reimbursement for an individual drug, but from a holistic and system perspective, I think awareness is gradually increasing.

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