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VALUE & OUTCOMES
SPOTLIGHT

A magazine for the global HEOR community.

Leveraging HEOR to Shape the Healthcare Landscape

ISPOR
Improving healthcare decisions

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JULY/AUGUST 2024
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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

TABLE OF CONTENTS

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Leveraging HEOR in Healthcare Systems Around the World

As of January 2024, 195 countries were recognized by the United Nations. Each of these countries has its own mechanism for managing healthcare/medical care. However, these typically tend to fall under 4 basic models of healthcare systems worldwide: the Beveridge Model, the Bismarck Model, the National Health Insurance Model, and the Out-of-Pocket Model.

A healthcare system governed by the **Beveridge Model**, named after William Beveridge, is government-provided and financed and similar to the United Kingdom's single-payer National Health Service. Countries using this model include the United Kingdom, Spain, New Zealand, Hong Kong, and Cuba.
The **Bismarck Model**, named after Otto von Bismarck, uses a nonprofit insurance system (the insurers are called "sickness funds") financed by employers and employees; examples of countries that utilize this model include Germany, France, Belgium, The Netherlands, Japan, and Switzerland. The **National Health Insurance Model** uses a single-payer national health insurance that combines private-sector providers with a government-run insurance program; countries utilizing this model include Canada, Taiwan, and South Korea. Lastly, the **Out-of-Pocket Model** (also referred to as "market driven" healthcare) is prevalent in less-developed countries where medical care is only accessible to the wealthy. The healthcare system in the United States is unique as it incorporates elements from all 4 models, varying based on factors such as age, employment status, and veteran status.

> Regardless of which model of healthcare systems is employed, it is important to understand how health economics and outcomes research (HEOR) can be utilized by healthcare systems around the world.

Regardless of which model of healthcare systems is employed, it is important to understand how health economics and outcomes research (HEOR) can be utilized by healthcare systems around the world to not only yield an economically viable and sustainable system for a country but, most importantly, to improve patient outcomes.

> By employing creative thinking, developing innovative and flexible approaches, and engaging appropriate stakeholders, a healthcare system's unique challenges can be addressed with particular and directed evidence-based solutions.

This issue of *Value & Outcomes Spotlight* includes 2 articles that demonstrate examples of how HEOR is making an impact in various healthcare systems.

Value Drivers in Health Technology Assessment: A European Perspective
The article by Muir et al discusses the complexities of harmonizing health technology assessment (HTA) across the European Union (EU). HTAs, traditionally focusing on clinical- and cost-effectiveness, are now expanding to include additional value elements. The Joint Clinical Assessment aims to standardize the pan-EU assessment process by 2025. However, variations in how EU countries apply value elements in HTA, influenced by their healthcare system's maturity and willingness to consider nonclinical value elements, pose challenges. Countries with more mature systems tend to include a broader range of value elements. To address these disparities, the authors suggest standardizing data collection and assessment methods, enhancing transparency, and promoting collaboration among EU HTA agencies. Standardizing these practices would ensure a more unified approach to HTA decision making and equitable patient access to treatments across the EU.

ISPOR Chile Organized the First National Ranking of Impactful Practices in Health Economics

In her article, Daniela Paredes-Fernández discusses ISPOR Chile Chapter's initiative to recognize and strengthen health economics practices in Chile, a country with a fragmented HTA system. ISPOR Chile developed the first National Ranking of Impactful Practices in health economics, highlighting innovative approaches and solutions using HEOR tools by various stakeholders, including public providers, insurers, and patient groups. The initiative awarded practices across 8 categories, including Management of Medicines and Medical Devices, Diagnosis-Related Groups, HTA, Health Innovation, Cost Analysis, Outcomes Research, Patient-Led Initiatives, and Other Health Impact Initiatives. The awarded practices ranged from improving access to affordable medications to implementing efficiency management models in clinics and developing advanced tools for pharmacotherapy safety.

This initiative has brought ISPOR and Chile closer to new stakeholders, fostering a culture of evidence-based health management in Chile. It has also strengthened ties with the Ministry of Health, the National Health Fund, and other decentralized bodies, laying the groundwork for future collaborations and innovative projects to improve the national HTA system.

These are just 2 examples of how HEOR has made an impact within these particular healthcare systems. With the variety of healthcare systems employed around the world, obviously no "one size fits all" HEOR approach can be developed to address their needs. Any HEOR solutions to the challenges posed by the country-specific system must be unique for that system. Clearly, the needs of each country's healthcare system necessitate individual consideration. By employing creative thinking, developing innovative and flexible approaches, and engaging appropriate stakeholders, a healthcare system's unique challenges can be addressed with particular and directed evidence-based solutions.

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

Mapping the Journey: Achieving Health System Sustainability

Rob Abbott, CEO & Executive Director, ISPOR

To suggest that healthcare is at an inflection point is to perfect the art of understatement. Across the world, health systems—the combination of people, institutions, resources, and activities whose purpose is to promote, restore, and maintain health—are struggling to deliver the best that medical science has to offer at a reasonable cost. Whether it's labor shortages within the healthcare sector, increasing complexity, rising numbers of patients with multiple chronic diseases amid population aging, or the onset of effective but expensive therapies (GLP1s and high-cost infusion drugs come quickly to mind), the long-term financial sustainability of health systems can no longer be taken for granted. It follows that the tremendous gains in health that have been achieved over the past 2 centuries can no longer be expected to continue unabated.[i]

> Across the world, health systems–the combination of people, institutions, resources, and activities whose purpose is to promote, restore, and maintain health–are struggling to deliver the best that medical science has to offer at a reasonable cost.

Within the United States, the much-discussed Medicare drug price negotiations, overseen by the Centers for Medicare & Medicaid Services, have overshadowed several other interesting and important developments on the healthcare landscape. These include retail giants Kroger and Wal-Mart increasing their health footprint. The former has transitioned in-store clinics to value-based primary care centers, while Wal-Mart has expanded its network of health centers and entered into a partnership with Orlando Health to make it easier for Orlando area residents and their providers to coordinate a patient's healthcare journey. Meantime, Amazon has acquired One Medical to build out its health portfolio to include selling healthcare services to employers; CVS has broadened its value-based primary care platform by acquiring Oak Street Health; and Costco has teamed up with Sesame to offer discount pricing on outpatient medical care.

If there is a unifying theme to these US-based developments, beyond nontraditional players increasing their positions in healthcare, it is a desire to make care more accessible and affordable to more people.

Against this backdrop, I'm both proud and excited about ISPOR's new 2030 strategy, which is anchored by a new vision: ***A world where healthcare is accessible, effective, efficient, and affordable for all***. As a professional society we want to leverage health economics and outcomes research (HEOR) evidence to help ensure that people have access to the care they need, when they need it, at a cost they can afford. This is not an easy lift. As the articles in this themed issue of *Value and Outcomes Spotlight* make clear, health systems across the globe are undergoing a period of unprecedented transformation, driven by technological advancements, demographic shifts, and rapidly evolving patient needs.

It should also be noted that our very conception of health is changing. Historically, it was approached largely in a physical context, but we know its meaning is much broader. And so it is that "social determinants of health" and "whole health" have rightly surfaced in the culture as better markers of what we are striving for when we speak of improving health and health systems. In this regard it is helpful to remember that the 1946 Constitution of the World Health Organization defined health as "a state of complete physical, mental, and social well-being." Again, I am pleased to see that the articles in this issue recognize the importance of improving all 3 of these component parts, as well as increased investments in prevention and the maintenance of good health. In this way, there is a tacit acknowledgement that good health is

> As a professional society we want to leverage health economics and outcomes research evidence to help ensure that people have access to the care they need, when they need it, at a cost they can afford.

fundamental for a high quality of life, as it influences our ability to truly enjoy life and participate in a wide range of daily activities. I would add that a core feature of ISPOR's 2030 strategy is broadening the definition of "value" in health decision making to include many of the defining features of whole health.

[i] For context, in the year 1800 no country in the world had a life expectancy at birth of more than 40 years. Today several European countries and Japan boast life expectancies that are double that. Many low- and middle-income countries have also seen considerable progress, but gaps remain, with life expectancies in some Sub-Saharan African countries below 60 years.

[ii] United Nations. *Delivering on the Global Partnership for Achieving the Millennium Development Goals*. MDG Gap Task Force Report 2008. Published August 2008. http://www.un.org/en/development/desa/policy/mdg_gap/mdg_gap_archive/mdg8report2008_enw.pdf

Another dimension of health systems across the world that I want to call out here is the need to ensure that people have access to essential medicines. This is fundamental and yet, as research from the United Nations shows,[ii] in many low- and middle-income countries the availability of medicines is much lower than in wealthier countries. This is a critical health equity issue and one that I personally take very seriously. As a global community we need to eliminate disparities in health systems and healthcare access. I'm therefore pleased to signal that a new ISPOR Special Interest Group is specifically examining how to accelerate access to novel medicines in these poorer countries.

In summary, I want to stress that despite the challenges facing global health, some of which I mention above, I'm optimistic. In fact, I consider it a great privilege to be alive at this time and to have the opportunity to lead an organization that is squarely dedicated to finding solutions to these challenges. We know that smart healthcare investments can improve health outcomes and that HEOR can inform those investments. We also know that health system change can happen quickly. In contrast to pioneering countries like France, Austria, and Germany—each of which expanded health system development and healthcare coverage between 1920 and 1960—China and Vietnam developed their healthcare systems in the 21st century and achieved significant progress in less than a decade. This demonstrates that real change is possible. ISPOR stands ready to leverage its global network to carry the momentum forward.

ISPOR SPEAKS

Transforming Healthcare Worldwide: ISPOR's Vision of HEOR Excellence for All

Eberechukwu Onukwugha, PhD, ISPOR President

As I step into the role of ISPOR President, I am honored to share my vision for our organization's future. My journey with ISPOR, which began in 2005, has been shaped by a truly global perspective, having lived and studied in the United States, Nigeria, and France. This international background has profoundly influenced my outlook on health economics and outcomes research (HEOR) and its potential to transform healthcare worldwide.

My personal history has taught me the importance of understanding the complex layers of identity and culture in healthcare decisions. For instance, the languages I speak—English, French, and Igbo—each connect me to different communities and perspectives. This diversity of experience informs my belief that we need to generate HEOR evidence that truly serves patients in all their complexity.

Furthermore, as we look toward the future, we must consider the demographic shifts projected for 2030 and beyond. For example, by the beginning of the next decade, individuals 65 and older will make up more than 20% of the populations of Europe, Russia, China, and the United States, while global population growth will be concentrated in parts of Africa and Southeast Asia. These trends underscore the need for innovative, globally minded approaches in our field.

> I am excited to introduce my vision for ISPOR's next chapter: "HEOR Excellence for All." This vision is not just a slogan, but a commitment to leveraging our expertise to improve healthcare worldwide.

Synthesizing these insights from my personal journey and our changing world, I am excited to introduce my vision for ISPOR's next chapter: "HEOR Excellence for All." This vision is not just a slogan, but a commitment to leveraging our collective expertise to improve healthcare worldwide. To fulfill this vision, we must focus on 3 key areas:

Catalyzing Innovation in HEOR
ISPOR has always been at the forefront of our discipline, and I believe we must continue to drive innovation. We need to push boundaries, explore new methodologies, and embrace emerging technologies to enhance our research and its impact. As the key driver of innovation in our field, ISPOR must lead the way in developing cutting-edge approaches to HEOR.

Advocating for Partnerships That Drive Innovation
I firmly believe that we can have a greater impact through strategic partnerships. By collaborating with diverse stakeholders—from patient groups to policymakers, from healthcare providers to technology innovators—we can bring HEOR solutions to the many challenges facing healthcare today and in the future. These partnerships will be crucial in expanding the reach and influence of our work.

Supporting Training for HEOR Professionals
Education and training are vital to ensure that our profession is well-prepared to make a lasting difference in healthcare. We must invest in developing the next generation of HEOR professionals, equipping them with the skills and knowledge needed to tackle tomorrow's healthcare challenges. This focus on professional development will be key to maintaining ISPOR's position as a leader in the field.

As we move forward, I am dedicated to making real progress in these 3 key areas. I will champion innovation that is truly meaningful—innovation that transforms our systems and transforms us. I will advocate for partnerships that reimagine the collection and management of real-world data, including what data we gather and who is represented. Finally, I will work to provide cutting-edge training for our worldwide HEOR family, particularly for students, junior investigators, and post-doctoral fellows. These commitments align with our goal of being prepared for the demographic shifts projected for 2030 and beyond.

I invite all ISPOR members and leaders to reach out, share your voices, and play an active role in realizing our collective vision of a world where healthcare is accessible, effective, efficient, and affordable for all. Together, we can shape the future of HEOR, ensuring that we are prepared to meet the healthcare challenges of tomorrow. By focusing on innovation, partnerships, and professional development, we can achieve HEOR Excellence for All. I look forward to working with you all as we embark on this exciting journey to make a lasting impact on global healthcare.

FROM THE REGIONS

Advancing ISPOR's Mission Through Local Chapters: Insights From the ISPOR Chile National Ranking of Impactful Practices in Health Economics

Daniela Paredes-Fernández, MPH, ISPOR Chile Chapter President

Why develop a national ranking of impactful practices from ISPOR?

Chile is an intermediate country in terms of its maturity in health technology assessment (HTA). At the regulatory level, there is no national body that organizes evaluation processes in a structured manner. Instead, its application occurs at the level of funding bodies. These funds organize mainly interim evidence evaluation schemes, in which industry often participates by presenting studies. Despite efforts from academia and key opinion leaders, Chile lacks a structured HTA system.

Regarding resource creation, capacity building for developing skills in HTA is concentrated in universities. However, there are a few formal educational programs that specialize in management, public health, and epidemiology, providing tools to enthusiastic professionals from the health sector who later apply these to the field of health economics. Additionally, the concentration of knowledge within academia has created a gap between some professional groups engaged in practical health system tasks and the academic segment, revealing a disconnect between providers, insurers, and the educational sector.

> The ISPOR Chile National Ranking aims to highlight the efforts of stakeholders currently applying HEOR methods to practical, everyday problems.

Those responsible for purchasing within the health system are currently supporting the implementation of the diagnosis-related group payment mechanism. They have limited capacity to implement risk-sharing agreements or other innovative schemes and insufficient ability to contribute to the HTA process in coordination with regulatory functions.

The lack of an HTA system in the country, the limited coordination between academia and regulatory bodies to generate evidence and local capacities, and fixed funding schemes have led to solutions emerging from stakeholders, emphasizing the need for ISPOR's international focus. In this landscape, concern arises among providers, private insurers, industry, patient groups, and startups to support their decisions with evidence.

Traditionally, health economics and outcomes research (HEOR) has been applied by HTA bodies, Ministries of Health, Social Security, and universities. However, HEOR's application extends beyond traditional stakeholders in contexts like Chile.

Thus, the ISPOR Chile National Ranking, organized by the new board of directors, aims to highlight the efforts of stakeholders currently applying HEOR methods to practical, everyday problems. The Chilean chapter proposes leveraging a work strategy with these new stakeholders to strengthen their capabilities.

Highlights from the ISPOR Chile national ranking

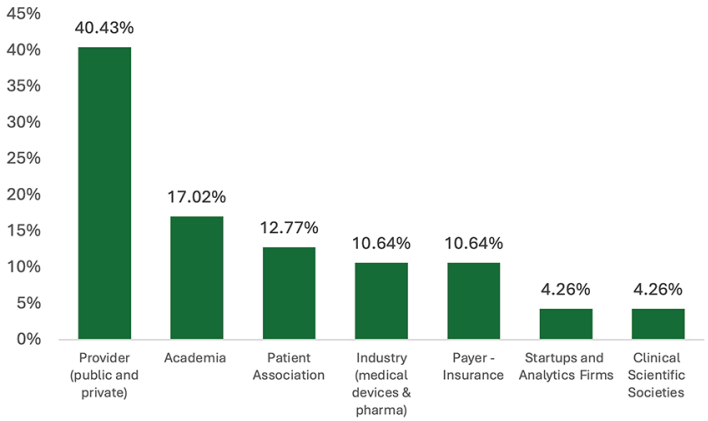
This biennial initiative is structured into a general ranking and various categories, where different health-related organizations within the healthcare ecosystem submitted their impactful practices across 8 categories, following rigorous submission guidelines. The evaluation process, conducted with a double-masked technique, meticulously weighs criteria for closing gaps through health economics tools, the technical characterization of impactful practices, and the benefits to both organizations and patients. A distinguished panel of judges, including prominent national and international experts in health science and economics (eg, academics, researchers, and leaders from other Latin American chapters of ISPOR), evaluated the initiatives, ensuring a comprehensive and high-quality analysis.

This initiative aimed to recognize the diversity of innovative approaches and creative solutions employing HEOR tools deployed by emerging stakeholders in the discipline's application. Identifying these stakeholders and their impactful practices allowed for the dissemination of often quietly performed practices within the community and the promotion of peer learning. Additionally, awards were given to attract talent to ISPOR, providing access to society memberships and short courses to enhance participants' capabilities and methodological rigor.

What impactful practices were awarded nationally?

More than 500 people joined this initiative. Each category awarded the top 5 impactful practices. Nineteen (40.43%) of the awarded organizations corresponded to public and private

Awards sorted by type of stakeholder.



providers, followed by 8 (17.02%) practices from academia. Six (12.77%) awards were granted to patient associations.

Below, we highlight the 8 organizations that achieved first place in their category.

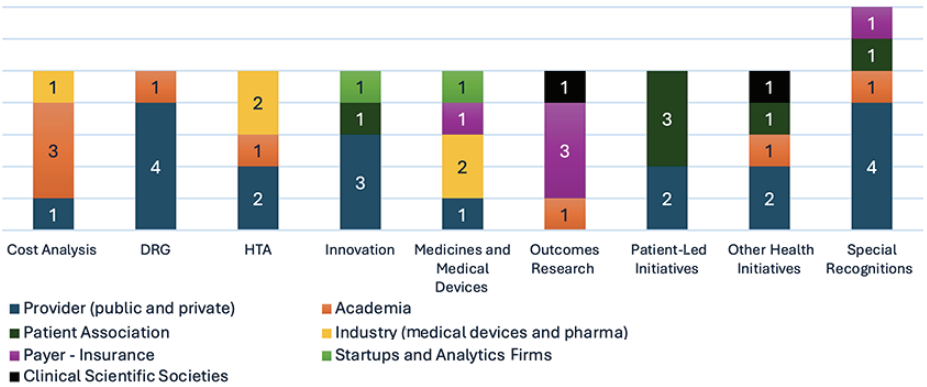
In the **Management of Medicines and Medical Devices category**, the award was given to the collaborative work between a private insurer (Seguros SURA SA) and the Chilean startup YAPP to improve access to affordable medications for patients. This initiative provides access to a digital platform for nontraditional pharmacies to reduce out-of-pocket medication expenses for Chilean families, optimize reimbursement processes, strengthen the financial sustainability of local pharmacies, and promote fair competition.

In the **Diagnosis-Related Groups category**, the award went to a private provider holding for implementing an efficiency management model based on diagnosis-related group use in RedSalud Clinics. This system's adoption has resulted in significant benefits, such as reduced average critical care unit length of stay, facilitated activity standardization, improved patient management, and network learning for knowledge transfer.

In the **Other Health Impact Initiatives category**, the award was given to a health policy analysis research project that helps mitigate factors explaining the over-medicalization of childbirth in Chile (ie, "Evidence and Recommendations for a Public Policy Ensuring Quality Childbirth Care" by the Chilean Society for Childbirth SOCHIPAR). This impactful practice addresses one of the clearest examples of supply-induced demand in Chile: the high rate of unnecessary cesareans. Evidence supports the idea that midwife-led units offer care with fewer medical interventions and are more cost-effective.

In the **Health Technology Assessment category**, the award went to the Universidad Austral for its practice of advanced tools for pharmacotherapy safety. This interdisciplinary work developed a supportive technological solution for establishing safe pharmacotherapeutic prescriptions. By implementing a real-time alert system, this practice aims to avoid unnecessary risks and therapeutic failures associated with inappropriate prescriptions.

Classification of winning stakeholders by category.



DRG indicates diagnosis-related group; HTA, health technology assessment.

In the **Health Innovation category**, Buho Chile was awarded for its system to optimize medication procurement and delivery through a technological algorithm that automatically compares prices among multiple pharmacies to improve access to lower-priced medications with home delivery across Chile. The wide price variability among pharmacies and the population's lack of tools for price comparison highlight the need for interventions that facilitate access to lower-priced medications.

> This initiative aimed to recognize the diversity of innovative approaches and creative solutions employing HEOR tools deployed by emerging stakeholders in the discipline's application.

In the **Cost Analysis category**, Roche was awarded for the merit of its cost-minimization and budget impact analysis of adopting the subcutaneous combination of trastuzumab and pertuzumab for treating HER2+ breast cancer in the Chilean public health system. This practice underscores the strategic role of cost-minimization studies from a health economics perspective, as they explore ways to further improve expenditure efficiency even in contexts with adequate treatment coverage.

In the **Outcomes Research category**, the award went to a private insurer (CONSALUD) for a practice focused on measuring economic sustainability and care quality through monitoring critical emergencies. Through active support, the insurer identifies inappropriate administrative or clinical practices that could lead to service overutilization, thus contributing to the system's financial efficiency.

In the **Patient-Led Initiatives category**, the award was given to the "Hospital in Your Neighborhood" initiative led by the public hospital of La Florida in partnership with the Patient Advisory Council. This practice highlights the importance of involving the community in identifying needs and improving care quality. Instances where users lead and coordinate activities to foster collaboration between the community and the hospital resulted in better resource utilization and care more focused on users' real needs, thus contributing to efficiency and equity in health service delivery.

The national ranking strategy has brought ISPOR and Chile closer to new stakeholders with whom we aim to build alliances and initiate innovative projects to improve national HTA. It has laid the foundations for a culture of celebrating evidence-based health management, bringing us closer to the Ministry of Health, the National Health Fund, and other decentralized bodies and strengthened ties with emerging stakeholders through joint projects and technical support. The initiative's novel approach has also garnered attention in the press. For more information, follow the discussion on LinkedIn here.

FROM THE REGIONS

Development of a Value-Based Payment Model for Patients With Osteoarthritis for the Bulgarian Healthcare System

[1]**Yoanna Vutova, MPharm**, HTA Ltd, Sofia, Bulgaria; **Slaveyko Djambazov, PhD, Plamen Kinov, PhD, DSc, Georgi Lukanov, BS**, ORFIO, Sofia, Bulgaria

Hip and knee osteoarthritis (OA) represents a significant global health challenge, affecting millions of individuals and leading to considerable disability and financial burden on healthcare systems worldwide. This chronic condition necessitates long-term management strategies, including surgical interventions such as arthroplasty, to alleviate pain and restore function. However, the increasing OA prevalence, coupled with rising life expectancies, is anticipated to further escalate the demand for these costly surgical treatments, which poses a substantial economic challenge.

In Bulgaria, the current stage of OA management involves significant waiting times for surgical procedures and varying rates of complications. Outcome assessment measures, such as the time to procedure and postsurgical complications, are tracked but not consistently integrated into a comprehensive quality-improvement framework. Although a local registry was established in 2022, it is not used consistently and could not serve as a reliable database for complication rates or performance measurement.

Current healthcare payment models, particularly fee-for-service, prioritize the quantity of care over the quality of outcomes achieved. This model incentivizes healthcare providers to increase the volume of services without measuring improvements in patient outcomes. As a result, patients may receive unnecessary treatments and experience avoidable complications contributing to inefficiencies, variable care quality, and increased healthcare spending.

> In Bulgaria, the current stage of OA management involves significant waiting times for surgical procedures and varying rates of complications. Outcome assessment measures are tracked but not consistently integrated into a comprehensive quality-improvement framework.

Recognizing the urgent need for reform, a team of value-based healthcare experts in collaboration with ORFIO, a prominent orthopedic nongovernmental organization with leading orthopedists, is poised to enact transformative change in Bulgaria's healthcare system. Our initiative targets the financial burdens and quality gaps inherent in OA treatment through the introduction of an innovative payment model for hip and knee arthroplasty. Our proposed solution involves the implementation of a bundle payment, designed to encompass the entire spectrum of OA care—from initial consultations to postoperative rehabilitation, inclusive of the most common complications.

The bundle payment model offers significant value for all stakeholders. For the payer (ie, National Health Insurance Fund [NHIF]), it provides a predictable cost structure and aligns payments with the quality of care, aiming to reduce overall healthcare spending by minimizing complications and unnecessary procedures. For the provider, it incentivizes the delivery of high-quality coordinated care, leading to better patient outcomes and potentially higher reimbursement rates linked to performance metrics. For the patient, value-based perspectives maximize outcomes, ensuring that care focuses on achieving the best possible health results rather than simply reducing costs.

Research and Results

The bundle payment covers the entire treatment cycle for patients with hip and knee OA undergoing joint alloplasty, including preoperative care, diagnostic imaging, hospitalization (excluding prosthesis), 3-month follow-up, treatment of the most common complications, and 14-day rehabilitation in the bundle price. Table 1 outlines the most common complications, respective frequencies, and target percentages associated with total knee and hip arthroplasty procedures included in the bundle price. The frequencies represent the expected occurrence of complications based on current data, while the target percentages indicate the desired reduction in complication rates following the completion of the 1-year pilot phase. The objective of the pilot phase is to establish an environment conducive to enhancing outcomes, promoting care integration, and encompassing the entirety of the care cycle. Therefore, some of the target values in **Table 1** are intentionally set to be achievable.

Table 1. Complication rate target for patients with OA undergoing surgical treatment.

Complication	Frequency, %	Target, %
Deep vein thrombosis	14,13 - 20,18[1-3]	18
Periprosthetic infections	0,8 – 1,9[4,5]	1,9
Periprosthetic fracture in primary arthroplasty	2,5[6]	2,5
Periprosthetic fracture in hip arthroplasty with mechanical fixation	5,4[7]	5,4
Periprosthetic fracture in hip arthroplasty with cement fixation	0,3[7]	0,3
Periprosthetic fracture in revision hip surgery	20,9[7]	20,9

The current practice involves fragmented care with separate billing for each service, leading to inefficiencies and higher costs. The new management pathway integrates all aspects of OA care into a single bundled payment, encouraging coordinated care and resource utilization. The bundle payment approach encourages healthcare providers to minimize complications, thereby reducing the additional costs associated with postoperative complications and inefficient treatment strategies, leading to an increase in overall value.

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To prevent selective bias, the program is risk-stratified and includes only healthy patients or patients with a minor medical condition undergoing surgical treatment, as defined by the American Society of Anesthesiologists (ASA) classification - ASA I and ASA II. Nonplanned events, such as unexpected complications or additional treatments, are incorporated into the payment scheme by setting aside a contingency fund within the bundle. The exclusion of prostheses is based on the variability in prosthesis choice and cost. This aspect will be reviewed and potentially included in future iterations of the bundle payment model based on feedback from the pilot phase.

Six Bulgarian hospitals will participate voluntarily for 1 year. At the end of the pilot phase, the program will be evaluated based on the feedback of the medical institutions that have participated and on an effectiveness analysis. The evaluation should determine whether the implementation of the program has led to improvements in clinical and important patient outcomes, whether other facilities will be included, or whether changes and adjustments are needed to achieve the objectives.

Key expectations include:
- Improved patient outcomes, including reduced complication rates and enhanced quality of life
- Cost savings for the healthcare system due to reduced complications and more efficient care delivery
- Increased provider engagement and satisfaction through aligned incentives and streamlined care processes

Limitations include:
- Initial resistance from providers accustomed to fee-for-service models
- Challenges in data integration and interoperability between different IT systems
- Need for comprehensive change management strategies to support the transition
- Long-term sustainability and scalability of the value-based payment model require further investigation

The outcome measurement is facilitated through the utilization of Bulgaria's arthroplasty register inaugurated in 2022. This resource is freely accessible to voluntary clinics participating in the initiative. The research methodology leveraged the Institutional Consortium for Health Outcomes Measurement standardized set for hip and knee OA treatments, encompassing a suite of measures that includes administrative, clinical, and patient-reported data.[8] Patient-reported outcome measures are regularly assessed through an innovative online messaging tool designed to streamline data collection and enhance patient engagement.

The stakeholders involved encompass a diverse range of actors, each playing a crucial role in the success of the initiative, including ORFIO, HTA Ltd team of value-based healthcare experts, healthcare facilities and providers, government agencies, NHIF, patients, and technology providers. All stakeholders collaborate and contribute to ensure the successful implementation and sustainability of bundle payments for patients with OA.

For the successful implementation of bundle payments for patients with OA in Bulgaria, a regulatory amendment will be made in the National Framework agreement between the NHIF and the Bulgarian Medical Union, which involves the establishment of a new clinical pathway tailored specifically to accommodate the requirements and protocols of the bundle payment model. This new clinical pathway encompasses guidelines, protocols, and standards of care designed to optimize the delivery of healthcare services within the framework of bundle payments. It outlines the sequential steps involved in the assessment, treatment, and management of patients with OA, ensuring consistency, efficiency, and quality throughout the care continuum.

Lessons Learned

The lessons learned through the development of the pilot program offer valuable guidelines for implementing such transformative healthcare models.

1. Utilizing standard sets proved instrumental in ensuring a consistent and meaningful assessment of treatment efficacy. This approach underscores the importance of standardized outcome measures in driving improvements in patient care and should be considered a best practice in healthcare reforms.
2. The adoption of bundle payments highlights several benefits, including fostering a more collaborative approach and encouraging innovation in care delivery to maximize efficiency and effectiveness. This model promotes a holistic view of patient care, aligning financial incentives with the achievement of positive patient outcomes. Incentivization stems from the fact that if it is not present, providers will bear the cost of treating complications.
3. Engaging healthcare providers and explaining the mutual benefits of the value-based payment model is crucial for its acceptance and success. Education and transparent communication about the goals and mechanics of the model facilitate buy-in from practitioners and administrative staff, showcasing the importance of stakeholder engagement in healthcare initiatives.

Challenges and Areas for Improvement

1. While the division of roles within medical facilities for data collection optimizes the process, integrating these data into a cohesive and actionable format poses challenges.
2. Transitioning to a value-based model requires significant changes in organizational culture and processes. Initial resistance from providers accustomed to the fee-for-service model is a notable challenge.
3. While the pilot program provides encouraging results, the long-term sustainability and scalability of the value-based payment model require further investigation.
4. The voluntary nature of the program's participation highlights the difficulty in achieving a critical mass of participating facilities. Moving forward, strategies to incentivize participation or demonstrate the value proposition of such models more clearly could help in overcoming this barrier.

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The implementation of a value-based payment model for OA treatment offers profound lessons for healthcare reform efforts. Best practices, such as focusing on outcome measurement, utilizing bundle payments, and engaging stakeholders are key drivers of success. However, addressing challenges related to data integration, managing the transition, and ensuring long-term sustainability is essential for the model's future adoption and impact.

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FROM THE JOURNALS

From Health to Well-Being: Toward a Monetary Valuation of a Well-Being Adjusted Life-Year

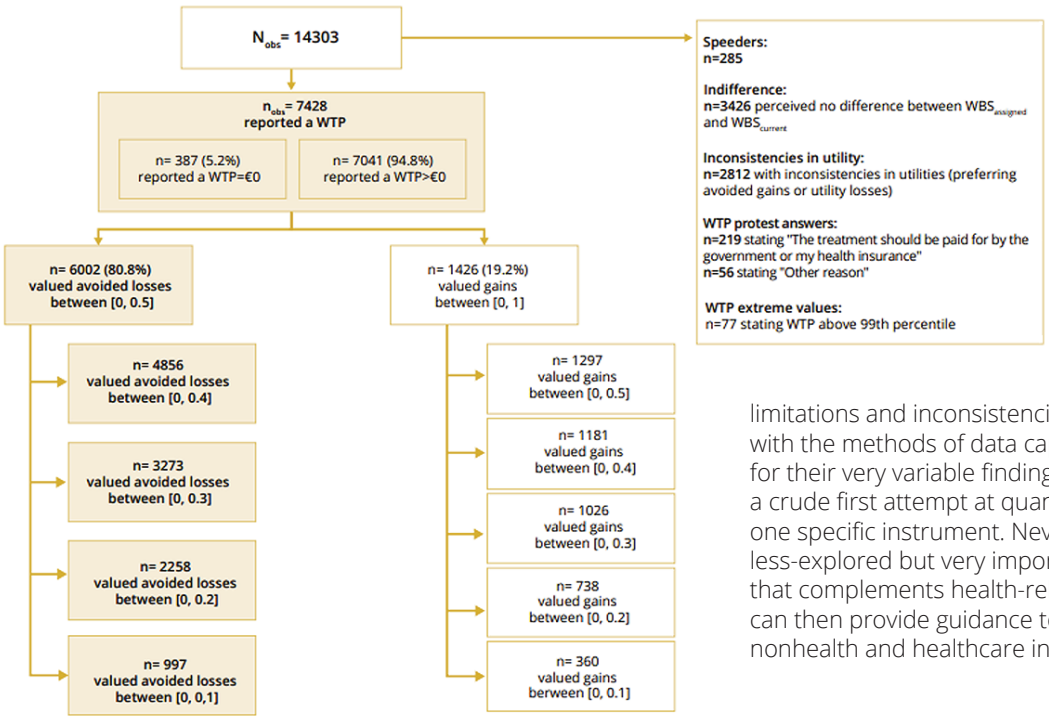
Brinkmann C, Stargardt T, Brouwer WBF. *Value Health*. 2024;27(7):857-870.

Section Editor: **Agnes Benedict**

Health-related quality of life and quality-adjusted life-year (QALY) has been the standard measure in economic evaluations and is now used widely in many countries for health technology assessment decision making. A broader concept, that of well-being, goes beyond health. Well-being has many different definitions, but a common one is that used in the ICECAP-A (the ICEpop CAPability measure for Adults tool,) focusing on domains, such as stability (ability to feel settled), attachment (ability to have love/ friendship and support), autonomy (ability to be independent), achievement (ability to achieve progress in life), and enjoyment (ability to experience enjoyment and pleasure) has been proposed and empirically measured using a variety of measures.

To aid decision making regarding resource allocations, the use of well-being-adjusted life years, or WALYs, similarly to QALYs, require an assessment of how much one unit of WALY is worth for society. This is the subject of the paper by Brinkmann, Stargardt, and Brouwer presented based on results of a large contingent valuation exercise, as part of the 11th and final wave of the European COVID Survey. Data were gathered from representative cross-sectional samples, with approximately 1000 adults from each of the following countries: Denmark, France, Germany, Italy, The Netherlands, Spain, and the United Kingdom, between November-December 2022.

Figure. Sample flow chart.



Valuations were done on changes in well-being relative to participants' current well-being score, using hypothetical examples. Participants were divided into 2 groups (see **Figure**). If a participant expressed a preference for the assigned well-being score over their current one, the participant was asked to imagine the opportunity to purchase a treatment that is approved, painless, and without side effects, that would get them to the assigned well-being state for a duration of 1 month. Vice versa, if the participant preferred their current well-being state over the assigned one, the participant was asked to imagine a sudden event that would lead to a loss of well-being to the assigned well-being state for 1 month and were told about a treatment that can prevent the loss. Their willingness to pay to access the treatment was explored. Full details of the methods are described in the paper.

Researchers restricted their analytical datasets to responses that were consistent, excluded participants doing the exercise too rapidly; made adjustments for cross-country differences in purchasing power, and took into account patients' different demographic and socioeconomic status (see **Figure**).

The authors found that only willingness to avoid the loss was consistent with expected behavior. Their main results suggest that a WALY may be valued as little at €13,000 or as high as €61,000 across the European population, depending on the specific change that was being valued. Smaller incremental changes traded off resulted in much higher willingness-to-pay values than large ones. Notably, the authors present a large set of subgroup specific results and regression analyses, providing a very good insight to the reader regarding the country-specific data and variability in individual preferences.

The paper is special in that it lists a very comprehensive set of limitations and inconsistencies transparently, pointing out issues with the methods of data capture, as well as potential reasons for their very variable findings. They acknowledge that this is a crude first attempt at quantifying the value of a WALY, using one specific instrument. Nevertheless, this study investigates less-explored but very important dimensions of quality of life that complements health-related aspects of quality of life, which can then provide guidance to resource allocation toward both nonhealth and healthcare interventions.

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Barcelona International Convention Center, Barcelona, Spain

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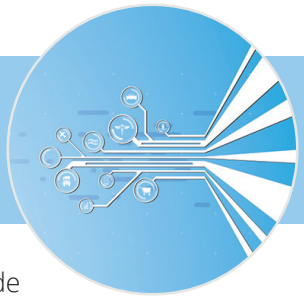

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After completing this course, participants will be able to...

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- Recognize and address ethical and regulatory considerations associated with LLMs and health data.
- Enhance decision-making processes to query health data with LLMs.

September 18-19 | 10:00AM – 12:00PM EDT (Virtual)

Introduction to Clinical Outcome Assessments: Selecting, Modifying, or Developing Fit-for-Purpose Measures

After completing this course, participants will be able to...

- Understand the value of measuring a patient-reported health status.
- Recognize different types of clinical outcome assessments (COAs).
- Gain knowledge of what each COA encompasses.
- Understand the properties of a good COA.
- Become familiar with the typical development and evaluation process for COAs.

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

Understanding Survival Modeling With Application to HTA

After completing this course, participants will be able to...

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

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Introduction to Best Practices for Country Adaptations of Economic Models

After completing this course, participants will be able to...

- Understand the importance of country adaptations at various stages of each pharmaceutical product's life cycle.
- Identify key country-specific factors that influence health economic evaluations and trigger model customization across countries.
- Determine appropriate data sources for country adaptations to capture accurate and relevant information for use in model adaptation.
- Incorporate country-specific data into existing economic models to estimate the economic impact within a specific target country.

17 November | 8:00 – 12:00 CET (In person at ISPOR Europe 2024)

Introduction to Applied Generative Artificial Intelligence (AI) for HEOR

After completing this course, participants will be able to...

- Understand the fundamentals of generative AI, particularly large language models.
- Navigate ethical and security considerations when employing generative AI in HEOR.
- Identify situations where generative AI can be used in HEOR.
- Execute generative AI models into HEOR applications through Python.

17 November | 8:00 – 12:00 CET (In person at ISPOR Europe 2024)

AI-Powered HEOR: Advancing Insights and Decisions with Large Language Models

After completing this course, participants will be able to...

- Discuss the advancement of generative AI and large language models and current applications of generative AI in HEOR.
- Explain the methodologies and tools used in AI-driven economic modeling and their advantages over traditional models.
- Develop strategies for integrating generative AI into regulatory decision making of external control arm.
- Utilize generative AI tools and techniques to perform advanced data analysis, manage large datasets, and synthesize real-world evidence for impactful healthcare solutions.

ISPOR Education

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Upcoming webinars include:

August 22 | 10:00AM – 11:00AM EDT

Moving Toward Universal Health Coverage in Africa: The Role of Health Technology Assessment

By participating in this webinar, attendees will...

- Acquire a deep understanding of health technology assessment (HTA) and universal health coverage (UHC) and their implementation challenges in Africa.
- Gain insights into practical examples of HTA application to inform priority setting and design benefits for UHC.
- Explore best practices in HTA implementation and the use of HTA for advancing UHC in the African context.

September 19 | 10:00AM – 11:00AM EDT

Transferability of Data and Methods to Central and Eastern Europe

By participating in this webinar, attendees will...

- Understand the potential benefits of transferability in methods and data, and considerations for applicability and transferability with the experiences and insights from the Central and Eastern European (CEE) countries.
- Explore ways to overcome barriers preventing optimal transferability of methods and data.
- Recognize the main barriers that prevent transferring data and methods in the CEE region.

October 9 | 10:00AM – 11:00AM EDT

Conducting Research and Survey Studies in Hard-to-Reach Populations

By participating in this webinar, attendees will...

- Understand the benefits of and barriers to involving hard-to-reach groups in survey and health preference research.
- Identify strategies for engagement of hard-to-reach groups.
- Review case study examples of how hard-to-reach groups have been involved in health preference research and important takeaways in terms of adaptations that can be made to recruitment strategies and survey tasks to improve engagement of hard-to-reach populations.

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HEOR NEWS

1 Relationship Between Health System Quality and Racial and Ethnic Equity in Diabetes Care (Health Affairs Scholar)

Researchers found racial and ethnic disparities in diabetes care quality in top-performing Veterans Affairs (VA) medical centers among American Indian or Alaska Native, Black, and Hispanic VA users versus White VA users. Read more

2 NHS Cancer Services and Systems: 10 Pressure Points a UK Cancer Control Plan Needs to Address (The Lancet Oncology)

This policy review discusses 10 key pressure points in the National Health Service in the delivery of cancer care services that experts say need to be urgently addressed by a comprehensive national cancer control plan, including increasing workforce capacity and its productivity, delivering effective cancer survivorship services, addressing variation in quality, fixing the reimbursement system for cancer care, and balancing of the cancer research agenda. Read more

3 Robust and Interpretable AI-Guided Marker for Early Dementia Prediction in Real-World Clinical Settings (eClinicalMedicine)

Building a robust and interpretable predictive prognostic model and validating its clinical utility using real-world, routinely collected, noninvasive, and low-cost patient data, researchers say they produced results that provide evidence for a robust and explainable clinical artificial intelligence-guided marker for early dementia prediction—one that is validated against longitudinal, multicenter patient data across countries, and has strong potential for adoption in clinical practice. Read more

4 Drug Development and Evidence for Lung Cancer Targeted Therapy in Eastern Asia (The Lancet Regional Health Western Pacific)

Researchers examine the development of genetic testing technology, targeted drugs approval, ongoing promising clinical trials in the field of lung cancer, and the important progress made by governments in the Eastern Asian region. Authors proposed key factors that will contribute to the promising future prospects in the region. Read more

5 Proportion and Number of Cancer Cases and Deaths Attributable to Potentially Modifiable Risk Factors in the United States, 2019 (American Cancer Society)

About 40% of all cancer cases and nearly one half of all cancer deaths in the United States in 2019 were attributable to the evaluated potentially modifiable risk factors, researchers say. The study notes that these findings reinforce that the morbidity and premature mortality from cancer in the United States can be substantially reduced through broad and equitable implementation of known preventive initiatives, such as excise taxes on cigarettes to reduce smoking, screening for and treating hepatitis C infection, and vaccination against human papillomavirus infection. Read more

6 MeDevIS Platform Announced to Boost Access to Medical Technologies and Devices (World Health Organization)

The online platform, Medical Devices Information System (MeDevIS), is the first global open access clearing house for information on medical devices. The platform is designed to support governments, regulators, and users in their decision making on the selection, procurement, and use of medical devices for diagnostics, testing, and treatment of diseases and health conditions. Read more

7 US Surgeon General Declares Gun Violence "a Public Health Crisis" (KFF News)

US Surgeon General Vivek Murthy declared firearm violence a public health crisis and called on policy makers to consider gun safety measures such as bans on assault weapons and high-capacity ammunition magazines and universal background checks for all firearm purchases. Read more

8 Next Leap in Modi 3.0: From UPI to a Unified Health Initiative (The Hindustan Times)

According to Ashwin Gopinath, cofounder and CTO of Biostate.ai, the recent election reaffirmed the country's faith in Prime Minister Narendra Modi's vision of a digitally empowered India. And it's time to envision the next frontier—a Unified Health Initiative that harnesses the power of artificial intelligence and digital tools to revolutionize India's healthcare landscape. Read more

9 CAR-T Cell Therapy's Complications, as Well as Its Benefits, Become Clearer in "Flurry" of Cancer Studies (STAT)

These papers give scientists a better idea of how often CAR-T patients go on to develop any subsequent malignancy and provide a blueprint for how clinicians might be able to detect the development of a potential CAR-T–induced cancer. Read more

10 1 in 10 People Infected During Pregnancy Develop Long COVID, Study Finds (Washington Post)

Nearly 1 in 10 people infected with the coronavirus during pregnancy developed long COVID, according to a study published in the journal *Obstetrics and Gynecology*, suggesting that long COVID is more prevalent among people infected while pregnant than in the population overall. Read more

HTA POLICY UPDATE

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

Welcome to the third edition of the HTA Policy Update, which provides a brief update on notable HTA policy developments from around the globe. We welcome suggestions and guest editorials for future issues; please contact the *Value & Outcomes Spotlight* editorial office with your ideas.

The Health Technology Assessment (HTA) Policy and Methods Review in **Australia** was concluded in May 2024. The purpose of the review was to reflect evolving HTA methods and assessment needs of novel health technologies and ensure continuous alignment with national policy objectives. The review examined HTA policy and methods with a focus on identifying areas for improvement to facilitate equitable access to new breakthrough medicines as early as possible and to deliver a strong and uninterrupted supply of the medicines Australians use every day.

HTA procedures and timelines in **Denmark** have changed as of April 2024. Under the new system, the old 16-week evaluation procedure has been replaced with 3 different processes, taking either 14, 16, or 18 weeks depending on the type of HTA application and specific circumstances of the therapy to be assessed. In addition, companies must specify a realistic application date ahead of the submission to facilitate coordination with available HTA review specialists and mutual agreement of an application date. The Danish Medicines Council (DMC) has also introduced a technical validation procedure to assess within 10 working days of submission whether applications meet formal requirements. The changes aim to expedite case processing and synchronize the HTA evaluation schedule with council and committee meeting dates.

In April 2024, FINOSE, the HTA collaboration in the **Nordics**, expanded further to include Iceland and subsequently renamed to Joint Nordic HTA Bodies (JNHB) in June 2024. The collaborating HTA bodies are the Danish Medicines Council (DMC), the Finnish Medicines Agency (Fimea), Landspitali - The National University Hospital of Iceland, the Norwegian Medical Products Agency (NOMA), and the Dental and Pharmaceutical Benefits Agency (TLV) in Sweden, representing all Nordic countries. The JNHB collaboration aims to support timely and equal access to medicinal products in the Nordic countries, reduce divergence in HTA methodologies and evidence requirements between the Nordic HTA bodies, share resources and knowledge, increase efficiency in generating assessment reports, and reduce the administrative burden for industry. JNHB recently entered into a collaboration with the Nordic Pharmaceutical Forum, thereby further integrating procurement and securing supply and quality of medicines in the Nordics.

After implementation of numerous amendments, the final draft of the Federal Government's Medical Research Act (MFG) in **Germany** was adopted by Parliament (Bundestag) in July 2024. The legislation aims to improve the conditions, remove bureaucratic hurdles and accelerate administrative processes for the development, approval, and manufacturing of medicinal products and devices in Germany. The controversial proposal for confidential pricing for new patent-protected drugs has been revised and clarified in the final draft of the bill: only manufacturers that conduct research in Germany will qualify for the option of confidential pricing at a standardized discount of 9% on the agreed price. Before the MFG comes into effect, currently planned for January 2025, it still needs to pass the German Federal Council (Bundesrat).

Italy's Medicines Agency (AIFA) has formed a new Technical Committee to support the Scientific and Economic Committee for Medicines in developing a process for the review of existing prescription frameworks in view of scientific evidence, medical care criticalities. Additional objectives are the development of alternative tools for governing prescription appropriateness and sharing AIFA's decision-making pathways with physicians and relevant scientific societies. The Committee is expected to deliver its results in January 2025.

Sweden's Ministry of Health and Social Affairs has commissioned the Dental and Pharmaceutical Benefits Agency (TLV) to investigate how health economic analyses can support a better understanding of the development of society's costs for modifiable risk factors for ill-health. The task for TLV is to examine the current public health policy monitoring system and propose enhancements by incorporating health economic principles, with the aim to optimize societal resources and enhance the efficacy of public health initiatives. TLV's final report is expected by the end of October 2025.

Taiwan has established the Center for Health Policy and Technology Assessment (CHAPTA) to assist in the HTA review of new health technologies. Having commenced its operations in January 2024, CHAPTA provides pharmacoeconomic assessments of new health technologies with the aim of establishing a national health insurance drug inclusion framework that reflects value and cost-effectiveness. Further, it conducts policy assessments and personnel training, and facilitates information and experience exchange with other international HTA organizations.

We are introducing a new section called "Methods Explained" in this issue of *Value & Outcomes Spotlight*, which will provide a high-level overview of a specific method based on the Section Editor's conversations with experts. Inspired by a keen interest in methods, the section aims to provide readers with an understanding of whether and when certain methods may be applicable to their work and offer a starting point for further reading. The column will cover the intent of the method, how it compares to alternatives, to what extent it has been implemented, and what challenges remain in its use and application. This first edition will cover multilevel network meta-regression and future editions may discuss methods like distributional cost-effectiveness analysis and best-worst scaling for stated preference research. Suggestions on topics to be covered and experts to be interviewed are welcome and can be shared with the *Value & Outcomes Spotlight* Editorial Office.

Multilevel Network Meta-Regression

Section Editor: **Koen Degeling, PhD**

For this edition of "Methods Explained," I have spoken to 2 experts who play an important role in the adoption of multilevel network meta-regression (ML-NMR) in the field of health economics and outcomes research (HEOR). Jeroen Jansen, PhD is an Associate Professor at the Department of Clinical Pharmacy of the University of California, San Francisco and Chief Scientist, HEOR at the Precision Medicine Group. Drawing on methods used in ecology, Jeroen first introduced a precursor to ML-NMR back in 2012.[1] David Phillippo, PhD is a Research Fellow in Evidence Synthesis at the Bristol Medical School of the University of Bristol. David generalized Jeroen's ideas into the ML-NMR framework and is the author of the multinma *R package, which is playing an important role in the broader adoption of ML-NMR.*

What is the objective of the method?

As an evidence synthesis method, ML-NMR aims to combine evidence from multiple sources to estimate relative treatment effects for decision making or research purposes in general. In many circumstances, multiple randomized controlled trials have been performed to estimate relative treatment effects and the evidence from these trials is to be combined. In doing so, there may be differences in population characteristics between studies that can impact the measured treatment effect. ML-NMR combines evidence from a collection of studies and accounts for differences in population characteristics to provide estimates of treatment effects between all treatments of interest. This aim of combining evidence from a collection of studies is conceptually the same as that of network meta-analysis, a well-known and widely used method in HEOR.

What makes it different from similar methods?

Standard network meta-analysis relies on aggregate data, such as estimates reported in scientific articles, and does not account for potential differences between the characteristics of the participants in clinical studies. This may result in biased estimates if such differences concern characteristics that impact the treatment effect, so-called effect modifiers. The "gold standard" approach is a network meta-regression combining individual-level data from every study, adjusting for differences in effect modifiers between study populations to provide unbiased estimates of treatment effects. However, it is rare for individual-participant data to be available for all studies and, often, a mixture of aggregate and individual-level data needs to be combined to consider all the evidence available. ML-NMR coherently combines both individual- and aggregate-level data, accounting for this common scenario where different levels of data are available from different studies (hence, "multilevel").

One could say that ML-NMR encompasses both aggregate-data network meta-analysis and individual-participant data NMR: it reduces to standard network meta-analysis when only aggregate data are used, and to the "gold standard" NMR if individual-level data are available for all studies.

For those that are familiar with evidence synthesis methods, this may sound like matching-adjusted indirect comparisons and simulated treatment comparisons. However, when using matching-adjusted indirect comparisons or simulated treatment comparisons, treatment effects can only be estimated for the study population as observed in the aggregate data. In other words, the target population in your research question has to be the same as the aggregate data study population for these methods to be useful. ML-NMR does not have this limitation. This is a very important benefit, because treatment decisions or conclusions may be different between populations with differences in their distributions of effect modifiers. Furthermore, matching-adjusted indirect comparisons and simulated treatment comparisons can only compare individual-level data studies to aggregate data from a single trial, whereas ML-NMR can combine individual-participant and aggregate data from any number of studies.

In summary, ML-NMR is different from other methods given that it is able to combine both aggregate and individual-level data and is able to provide effectiveness estimates for a target population that is relevant to the research question and does not have to match that of the aggregate data used.

What are the steps involved in applying the method?

On a high-level, the steps for performing a ML-NMR are the same as those for a network meta-analysis: defining the

research question, deciding on the model to use, gathering the data, running the analysis, and assessing the impact of key assumptions. However, certain aspects must be more explicitly and transparently defined, mainly the selection of effect modifiers and the definition of the target population of interest.

Running an ML-NMR can be considered more complex compared to running a standard network meta-analysis, which can be easily done in various software. This has likely been a barrier to the broader adoption of ML-NMR. With the publication of Phillippo's *multinma* R package, a relatively user-friendly approach is offered for running ML-NMR analyses in a software that is commonly used for other evidence synthesis and data analysis tasks.

To what extent has the method been used in practice?
Although ML-NMR is recommended by the National Institute for Health and Care Excellence (NICE) Decision Support Unit in the United Kingdom as a preferred method for population-adjusted indirect comparisons,[2] there have only been a few applied examples across disease areas. For example, it was used in NICE TA912 that evaluated cipaglucosidase alfa with miglustat for treating late-onset Pompe disease, where it was well-received by the Evidence Assessment Group.[3] Given the important advantages it has over other methods and with the introduction of the *multinma* R package, the number of applications is expected to increase over the coming years.

What is next for the method?
Given that other methods like matching-adjusted indirect comparisons are better known and well-understood, broader awareness of ML-NMR and an improved understanding will be important to ensure the HEOR community can leverage the advantages it provides.

Different extensions of the method may further increase its applicability. For example, Jansen and Phillippo particularly see value in facilitating parameterization of full multistate models, which are a particular type of decision-analytic model that can be used to evaluate the health and economic outcomes of different healthcare interventions. Another opportunity lays in the incorporation of single-arm trials and disconnected evidence networks, which is highly relevant given the increased use of single-arm studies in particular disease areas.

What are some key references for further reading?
Those who would like to learn more about ML-NMR may have interest in reading a "walkthrough" paper based on a case study in plaque psoriasis[4] or a more foundational paper.[5]

Did you enjoy reading this article? Or do you have any suggestions for methods to be covered in future editions? Please share your feedback with the *Value & Outcomes Spotlight* Editorial Office.

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LEVERAGING HEOR TO SHAPE THE HEALTHCARE LANDSCAPE

By Christiane Truelove

In an era of unprecedented medical advancements, healthcare systems worldwide face a paradoxical challenge: delivering cutting-edge treatments while ensuring affordability and accessibility. Healthcare systems are struggling to deliver optimal medical care at reasonable costs. Factors such as labor shortages, aging populations with multiple chronic diseases, and expensive new therapies threaten the long-term financial sustainability of health systems. Moreover, the disparity in access to essential medicines between high-income and low- and middle-income countries highlights a critical health equity issue that demands urgent attention.

It's clear that one size doesn't fit all when it comes to healthcare systems and how to achieve the goals of better health and outcomes for all patients.

The World Economic Forum outlines 4 types of healthcare systems: universal coverage with a single-payer system (the Beveridge model); universal coverage with a multipayer system (referred to as the Bismarck model); the National Health Insurance model (which combines elements of the Beveridge and Bismarck models); and no national healthcare infrastructure (fully out of pocket). During the COVID-19 pandemic, all of these systems were stressed in the face of unprecedented demand. Discussions in the wake of the pandemic have focused on making health systems more resilient and better positioned to best utilize resources. The main challenge is even in economically strong countries using a universal healthcare system, there may not be enough resources to provide healthcare due to factors such as aging populations with chronic healthcare conditions unable to pay taxes or work.

Breaking down the systems: Beveridge, Bismarck, National Health Insurance, others

Under the Beveridge model, healthcare is funded by direct income tax deductions, with the majority of hospitals owned and operated by the government, and the state employing most healthcare staff, including doctors and nurses. The most familiar incarnation of this is the United Kingdom's National Health Service, and the model takes the name of the economist Sir William Beveridge, who first established it in 1948.

> "Approximately 76% of hospital beds in India are in the private health system and 24% within the government system."
>
> – JK Sharma, PhD

This type of system is also found in Spain, Brazil, Cuba, and New Zealand. The main advantage of this type of system is by having the government as the sole payer, costs can be kept low and benefits standardized. However, because everyone can access the services, overutilization can create constraints such as timely access to healthcare staff and procedures. And in times of crisis, such as the pandemic, a decline in funding may exacerbate the financial burden created by additional patients.

The Bismarck model was created at the end of the 19th century by Otto von Bismarck. It is a decentralized form of healthcare where employers and employees fund insurance through mandatory payroll deductions. All money goes into "sickness funds" that are accessible to all employed, plus there are private insurance funds that cover every insured person. Countries that have this type of system include Germany, France, Belgium, the Czech Republic, and Japan. Health providers are generally private institutions, although the Social Health Insurance funds are considered public.

> "When considering how to subsidize care for the population that is buying healthcare on an 'as needed' basis, India will need to decide whether to follow the UK or US model."
>
> – JK Sharma, PhD

Because the Bismarck model is not a universal healthcare model and is geared towards providing benefits to the employed, those who are not employed or cannot contribute financially are overlooked. There are other strains as well. In Germany, the country is in the process of major healthcare reforms to tackle problems such as too few doctors (especially in rural areas), too many empty hospital beds, and too much financial pressure on hospitals. Among the proposals under Health Minister Karl Lauterbach are a two-pronged hospital reform under which hospitals will no longer be paid per treatment but get a guaranteed income for making certain services available. Officials hope this will alleviate the financial pressure on hospitals to book as many operations and treatments as they can and get people who need more complex treatment referred to specialists earlier. Not only is this expected to save lives, but also reduce health costs in the long run, as patients stand a better chance of being cured and are less likely to fall victim to mistakes caused by rushed and overworked hospital staff.

The National Health Insurance model combines elements of the Beveridge and Bismarck models. In this type of system, the government funds healthcare services, which are paid for through taxation, similar to the Beveridge model. The delivery of healthcare services is provided, however, mostly through private organizations, similar to the Bismarck model. Canada is the most notable example of this kind of system. Healthcare is funded and administered primarily by the country's 13 provinces and territories, with each having its own insurance plan and receiving cash assistance from the federal government on a per capita basis. Benefits and delivery approaches may vary from province to province, but all citizens and permanent residents receive medically necessary hospital and physician services free at the point of use. Other countries using the National Health Insurance model are Australia and New Zealand.

The out-of-pocket/uninsured model means that there may be no organized healthcare system, or that private insurance is too expensive, and those who need treatment pay for it out of pocket. This system is found primarily in low-income countries that lack the resources to fund a strong healthcare system. Many countries in sub-Saharan Africa fall within this category, as well as rural areas in low-income countries where publicly funded or nongovernmental organization healthcare facilities are lacking.

A multimodel healthcare system: The United States

The United States has a fragmented healthcare system, as outlined by the Commonwealth Fund, in which funding and availability are dictated by type of insurance. For those on Medicare, the Indian Health System, and the Veterans Administration (VA) system, their healthcare is funded by the federal government; Medicaid is funded by the state governments. Medicare and Medicaid patients, however, receive treatment through private healthcare facilities and doctors, with these systems more in line with the National Health Insurance model, and VA and Indian Health Service patients receive their treatment through government facilities, in line with the Beveridge model. However, private and employer-, and employee-funded health insurance remains the predominant form of coverage. According to the Commonwealth Fund, two-thirds of Americans, or 67%, have private insurance as their health coverage as of 2018, However, the uninsured rate for adults aged 19 to 64 was 12% in 2018, down from 20% in 2010 when the American Care Act went into place.

> "We also look at catalyzing policy change to make the right things to do easier to do."
>
> – Jennifer Zelmer, PhD

As health systems worldwide grapple with sustainability and accessibility challenges, 2 contrasting examples—India and Canada—offer valuable insights into the complexities of modern healthcare. India's healthcare system provides a compelling case study of the challenges faced by emerging economies. Canada offers a different perspective on addressing healthcare challenges, focusing on rapid adoption of proven innovations and policy changes to improve healthcare quality and safety.

Working to improve coverage

Health Coverage in India

According to JK Sharma, PhD, president and CEO of Andhra Pradesh Medtech Zone (AMZT) Ltd and a former head of health financing for the Ministry of Health, India's healthcare system falls into a category similar to Thailand, where the government is working towards universal health coverage but does not have enough resources to take care of all of its citizens, at least not initially. "That leaves countries like India in a difficult position where they have to choose the manner in which they cover their people," he says.

India currently has an "extremely robust" private healthcare sector and a "fledgling" public health sector, according to Sharma. He estimates that approximately 76% of hospital beds in India are in the private health system and 24% within the government system. For those government patients, the public sector provides nearly 45% of healthcare, and for patients in the private health system, the private sector provides 55% to 60% of care.

> "One of the expectations is that we engage patients, families, residents, and others with lived experience in that work."
>
> – Jennifer Zelmer, PhD

Patients in India generally fall into 4 categories. The first are those below the poverty line, making less than $2500 a year. The second are people above the poverty line who are either paying for private insurance or their employer is paying. The third comprises public government employees who can go to government hospitals and receive free care. The fourth—and largest—category is people who pay out of pocket and have no insurance. This category comprises almost 60% of patients.

Sharma says India's government is not worried about people whose care is funded by the government. Instead, India is concerned about the patients who are not covered by private or government insurance and paying for care out of pocket. "When considering how to subsidize care for the population that is buying healthcare on an 'as needed' basis, India will need to decide whether to follow the UK or US model."

Health economics and outcomes research (HEOR) can provide a "pragmatic way" to gather information so the government can make decisions on coverage. Although there are no data being gathered on the out-of-pocket population, "patients below the poverty line that receive government-funded care can generate evidence to determine which populations to cover in future," Sharma says.

For example, India does not cover insulin for the treatment of diabetes; instead, patients buy it out of pocket. The country has some evidence from a systematic review that looks at what would happen if insulin pens are provided. Besides considering whether a government program should offer syringes (which are cheaper but are historically disliked by patients) or pens (which are more expensive but are easier to administer and safer), "should it cover people over the age of 50, which

represents the biggest portion of the diabetic population? Should it cover people over the age of 40, which would include more people, or should it include patients who are 30 years old, which may even include type 1 diabetes?" Sharma asks. "We have the evidence from patients in the private sector and are looking at projecting that evidence for everyone and evaluating the budget impact."

Innovative Approaches in Canada

Jennifer Zelmer, PhD, is CEO of Healthcare Excellence Canada, a nationwide charity that works with partners to spread innovations, build capability, and catalyze policy changes so that everyone in Canada has safe and high-quality healthcare. According to Zelmer, most of the organization's efforts are focused on rapid adoption of proven innovations.

When it comes to innovation, the organization is not looking for technologies, but policy changes, program and model changes, changes in scope of practice, "whatever is required to improve quality and safety at the end of the day." For example, Healthcare Excellence Canada is working with long-term care homes to support both stronger person-centered care and supporting and retaining the workforce in that environment. Another example would be safety-effective care transitions from hospital to home, to reduce the number of hospital readmissions, Zelmer says.

The HEOR community plays a crucial role in addressing these global healthcare challenges. Don't just observe the changing healthcare landscape–shape it.

"We recognize that if we only work on innovation by innovation, we're going to be at this for a very long time," Zelmer says. Healthcare Excellence Canada aims to build capacity in the health system for effective engagement with patients and frontline workers, as well as strong leadership and governance. "Local teams can do amazing work, but if they're trying to do that work in policy or structural contexts, that makes it difficult. They're pushing water uphill," Zelmer says. "We also look at catalyzing policy change to make the right things to do easier to do."

All of these innovations need to be supported by evidence, and that means real-world evidence is "critically important," and Zelmer expects the organization to "continue doubling down and using real-world evidence as part of the work that we do." She adds that Healthcare Excellence Canada would be following the position set by Health Canada on Canada's Drug and Health Technology Agency Guidance for Reporting Real-World Evidence that was made effective in 2023.

The organization also believes in working with patients to gather real-world data. "For instance, one of the expectations is that we engage patients, families, residents, and others with lived experience in that work," Zelmer states. "We have a network of patient partners we work with and we work to build the health system's capacity and expertise in being 'engagement capable.'"

These contrasting examples from India and Canada highlight the diverse challenges and approaches in global healthcare. They raise important questions about resource allocation, the role of public and private sectors, and the importance of evidence-based decision making in healthcare policy.

Shaping the Future of Global Healthcare

The HEOR community plays a crucial role in addressing these global healthcare challenges. As experts in evaluating the economic and clinical outcomes of healthcare interventions, HEOR professionals are uniquely positioned to drive evidence-based decision making and policy formulation. Don't just observe the changing healthcare landscape—shape it.

- Intensify research efforts in low- and middle-income countries to provide robust data for healthcare policy decisions.
- Develop innovative methodologies that can capture the complexities of diverse healthcare systems and populations.
- Collaborate across borders to share best practices and insights that can inform global healthcare strategies.
- Engage with policy makers, healthcare providers, and patient groups to ensure that HEOR findings are effectively translated into practice.
- Advocate for the integration of HEOR principles in healthcare decision-making processes worldwide.

By rising to these challenges, the HEOR community can play a pivotal role in shaping a future where innovative, accessible, and sustainable healthcare is a reality for all.

By the Numbers: Healthcare Systems Around the World

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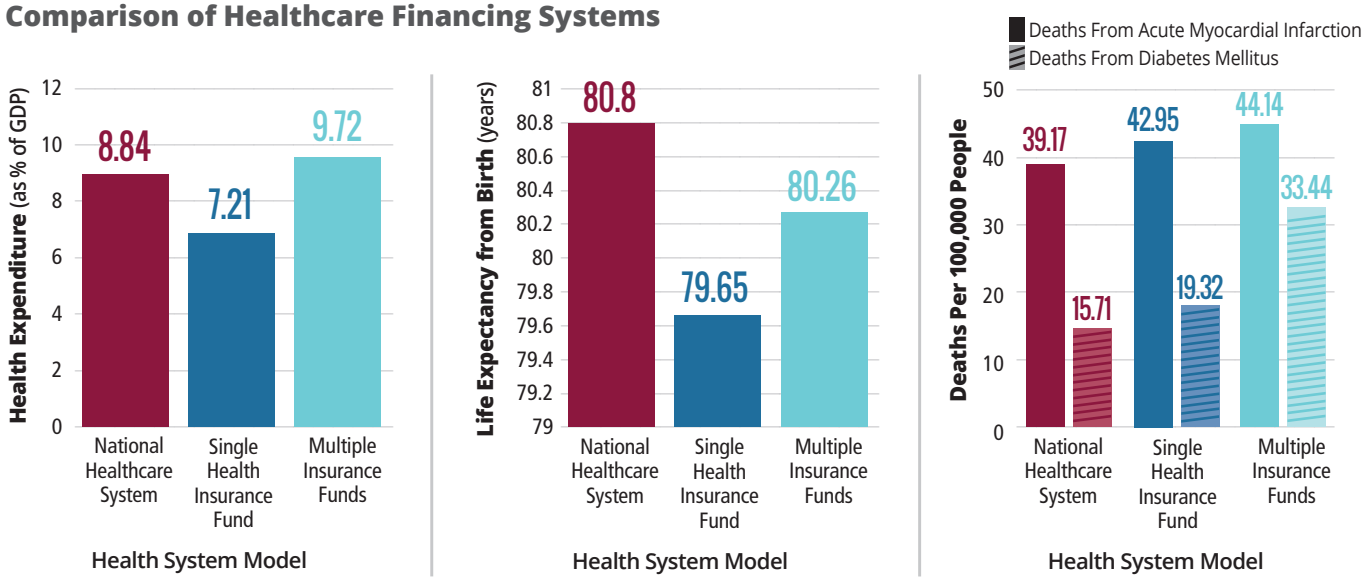
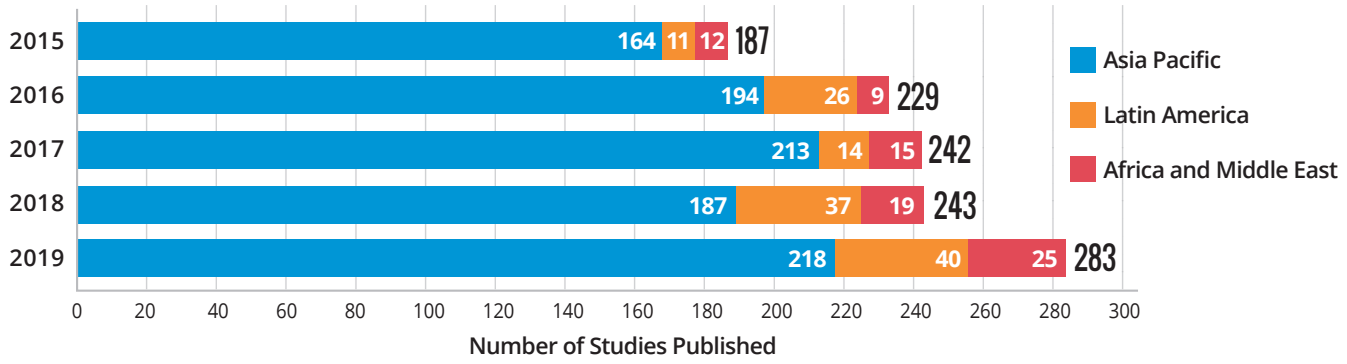
Comparison of Healthcare Financing Systems



Real-World Oncology Studies in Emerging Economies Published Between 2015-2019



Impact of Smartphones on Generating Real-World Data for Healthcare Systems

95% of Americans have a **cell phone**

75% of patients are **willing** to use mobile tools or **telemedicine**

20% of Americans have **online access only** through a **smartphone**

75% of physicians are using **mobile tools** in their clinic

Institutional Country-Specific Context and Value Drivers in Health Technology Assessment: A European Perspective

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Efforts to harmonize the health technology assessment process in the European Union are hindered by jurisdictional differences in healthcare system implementation and value determinants when assessing new therapies.

A more standardized approach to incorporating additional value elements, such as the broader societal and environmental impact of technologies, is needed.

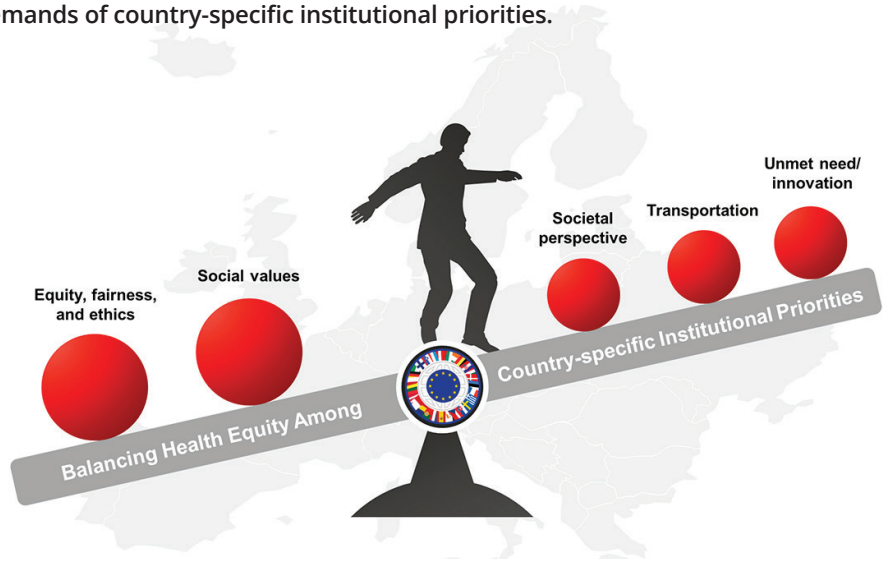
An improved understanding of the drivers of health technology assessment is needed to ensure equitable access to treatment.

Health technology assessments (HTAs) are a cornerstone of healthcare decision making across many countries, each of which applies various context-specific criteria in their evaluations. Traditionally, clinical- and cost-effectiveness are the main drivers of determining the added value of a new treatment. Recently, though, there has been an effort to expand the elements considered during HTA, with an added focus on what are considered "additional" elements of value.[1] This can be considered an extension of the "go beyond health" concept championed by Engel et al,[2] who first suggested that HTA agencies consider factors beyond the mere improvement of health outcomes when evaluating new therapies (**Figure 1**). The challenge in incorporating these additional elements in multijurisdictional HTA efforts, however, is to achieve a fully harmonized approach in a climate where criteria outlining what constitutes "value" and the methods to assess these value elements differ from country to country.

This challenge is especially prescient in the European Union (EU), where the 27 member states each apply their own criteria and evaluation processes, involving varying regulatory bodies and jurisdictional differences[3] and complicated by the differing approaches to healthcare system design throughout the European Union.[4] Indeed, much effort has been spent examining access to healthcare and the inequities that exist across the different EU member states,[5] towards a goal of providing equal access to all citizens, regardless of socioeconomic standing.[6] In an effort to standardize the pan-EU assessment process, the Joint Clinical Assessment (JCA) has been proposed.[7] This effort seeks to provide a common approach to HTA, one designed to create efficiencies and accelerate the availability of new treatments across European citizens. The proposed JCA will provide a uniform set of factors to assess the clinical value of new technologies while leaving interpretation of the findings to be jurisdiction-specific, such that each HTA body would remain responsible for determining the potential added value of a therapy based on their specific healthcare system.[7]

Full implementation of the JCA guidelines is slated for early 2025; however, in the lead-up to this, it is important to evaluate the current decision-making climate and,

Figure 1. Elements addressing health equity must be balanced against the demands of country-specific institutional priorities.



in the context of additional aspects of technology value, to determine what elements are currently considered as part of the various HTA agencies. The published literature reveals wide variations between EU member states on the decision criteria and suggests, among other determining factors, that 2 main considerations will govern the ease with which the JCA guidelines will be accepted: (1) the willingness of a member state to include elements of value beyond clinical effectiveness, and (2) the institutional context for each member state.[8]

> There has been an effort to expand the elements considered during HTA, with an added focus on what are considered "additional" elements of value.

Willingness to Include Elements of Value

Value elements beyond the purely clinical or economic are numerous and varied. Novel value elements include factors that can be quantified directly (such as environmental impact, productivity, transportation, etc) as well as factors that are perceived as less quantifiable (such as the value of hope, real option value etc.). Several of these novel elements are widely reported in the literature and thus represent core values considered by many countries, while others are more rarely included and could be considered emerging philosophical topics. Among EU member states, equity or fairness sits atop the list. Elements that consider the social value of a new therapy or whether the social perspective is addressed by a new therapy were also frequently considered. These 3 elements could be grouped loosely under the umbrella of "societal considerations," as they examine the impact of a potential new therapy on society itself and are widely recognized. The societal net could be cast farther to include several other elements that are relatively commonly incorporated: whether the therapy will impact society's (and patients') productivity, whether indirect factors are taken into consideration, and whether the therapy will impact transportation within a society (ie, the ability of that society to continue to be mobile). In the European landscape, these elements—all of which address the impact of a new therapy on the societal fabric—are often considered, suggesting that their value is real and recognized. There are a number of elements that are, in contrast, considered by very few countries. Elements such as environmental impact, adherence-improving factors, and disease severity are considered intermittently, indicating that their value cannot be clearly established in a broader multijurisdictional framework and thus would require reconsideration or further research to determine their real value. Finally, there are elements of value that may be considered "emerging elements" that are considered very rarely.[1,9] Interestingly, these elements tend to reflect a societal perspective and the value of a given therapy for the patient and their overall well-being, beyond that which is provided by the therapy. As such, their rare inclusion is curious, as they fall under the umbrella of elements that have historically been viewed as important. Real option value, or the potential benefit from other interventions realized by extending the patient's life, is rarely considered. While other elements such as the value of hope and the reduction of uncertainty—valuable elements that may not realize a tangible return on investment but nevertheless provide patients with hope and thus may provide an additive factor to a new therapy—are almost never mentioned. This also holds true for the impact of a given therapy on the capacity of the healthcare system. That these elements are considered in such low numbers, especially given their societal impact and the obvious value of societal perspective to most EU member states, represents a missed opportunity in HTA decision making.

Elements of Value and Institutional Context

Constitutional context exerts substantial influence over the incorporation of elements of value into HTA decision making. There is evidence that the maturity of the healthcare system in part governs the ability to incorporate additional elements of value, with less mature HTA organizations often "lacking the expertise and resources to assess societal and novel elements."[10] Of the 25 EU member states where research data are available, 9 have a Beveridge-type national healthcare system, 8 have a social health insurance system based on the Bismark model, and the remaining 8 have a system that would be considered "in transition."[4] Perhaps not unexpectedly, countries with a robust national health system tend to incorporate more elements of value, whereas countries with systems in transition consider fewer elements. Countries using a social health insurance system offer a more robust offering than those in transition but do not match the commitment of national healthcare system-style countries.

Regardless of institutional context, there is some consensus among EU member states on the most important additional value elements, namely equity/fairness and social values. Likewise, societal perspectives and unmet needs are considered in the vast majority of countries, regardless of healthcare system. Where things diverge is in the incorporation of the "second tier" of societal elements, such as productivity considerations, transportation impact, etc. Countries with more mature, robust healthcare systems tend to incorporate these elements, while those in transition do so much less frequently. This trend is even more noticeable in the context of emerging elements that tend to be considered in only the most robust and comprehensive countries.

> There is substantial variation in how different EU member states apply elements of value in HTA, which only adds to the challenges associated with applying a uniform set of standards to a diverse and varied group of jurisdictions.

Clearly, there is substantial variation in how different EU member states apply elements of value in HTA, which only adds to the challenges associated with applying a uniform set of standards to a diverse and varied group of jurisdictions. The incorporation of additional value

elements into HTA decision making will also require sufficient and suitable data which are unlikely to be available across all jurisdictions. The willingness of a member state to adopt elements beyond the merely clinical and/or economic in HTA deliberations is at least partially tied to the healthcare construct employed by that country. We have seen that countries with more mature and robust health systems are more willing to broaden the criteria used in their discussions, perhaps with the understanding that, as the main funder of the system, their willingness to consider a broad range of factors may ultimately result in better outcomes and therefore improve the return on their investment. Conversely, countries with systems in transition have been seen to take a minimalist approach and look essentially at unmet needs alone. This is perhaps not unexpected for countries in transition, although it does underscore the challenge of applying the JCA guidelines on a broad scale.

Lessons Learned

There are challenges ahead in the implementation of the JCA guidelines for HTA agencies in the European Union. The current jurisdictional differences in institutional design and value drivers create disparities among the member states that create inequalities for their citizens. Understanding and addressing the variability of HTA acceptance drivers at a more granular level is key from the perspective of equal patient access to (innovative) treatments across Europe, to ensure that different trends in value considerations between national assessments do not threaten the weight of EU JCA in local HTAs and decision making. Chief among the challenges ahead is the variability of value considerations across national assessments within the European Union, with member states prioritizing various aspects of value. While the use of clinical and cost-effectiveness is widespread across the European Union, other elements, such as equity, fairness, social value, environmental impact, productivity, and the value of hope are only considered sparingly and in varying degrees. This diversity in value drivers can lead to discrepancies in the evaluation of new treatments and ultimately to patient access.

> Sharing best practices, lessons learned, and successful strategies for incorporating diverse value elements can promote a more unified and effective approach to HTA decision making.

To overcome these challenges, HTA agencies must aim for a more harmonized approach that considers a comprehensive range of value elements. Standardizing data collection methods and assessment frameworks can facilitate meaningful comparisons and ensure the credibility of HTA outcomes across member states. Efforts should also focus on enhancing transparency and collaboration among HTA agencies within the European Union. Sharing best practices, lessons learned, and successful strategies for incorporating diverse value elements can promote a more unified and effective approach to HTA decision making.

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The Role of External Control Arms in Drug Development and Considerations for Success

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Strong justification for the use of a single-arm trial and corresponding external control arm study is needed when deviating from randomized controlled trials, which remains the gold standard to evaluate efficacy of new products.

Discuss external control arm study plans early and often with regulators to align on the anticipated study and ensure their feedback is incorporated into the design, methods, and data source selection.

Selection of the external data source in an external control arm study should be supported by a systemic and rigorous fit-for-purpose data source evaluation.

Careful consideration during the study design phase is needed to avoid or mitigate biases such as confounding, selection bias, immortal time bias, and a lack of comparable outcomes.

Introduction

External control arm (ECA) studies are typically pursued to meet evidentiary standards of regulatory and/or health technology assessment (HTA) bodies and developed to complement single-arm trials. While randomized controlled trials (RCTs) are the gold standard for decision-making, ECA studies can be a valuable tool under appropriate circumstances. Strong justification for the use of a single arm trial and corresponding ECA study is needed for submissions to regulatory and HTA bodies. Circumstances that may necessitate a single-arm trial rather than a RCT include debilitating or life-threatening diseases with no available treatment, enrollment challenges, or where clinical equipoise does not exist. In an ECA study, patients from an external data source are carefully selected to represent the clinical trial target patient population, and then the ECA patients are indirectly compared to patients in the single-arm trial. ECA studies have been used to demonstrate the efficacy of experimental therapies, most commonly for some types of cancer and rare diseases.[1]

> There has been a growing interest in the use of ECA studies and their potential impact on drug development.

Typical external data sources used for ECAs include prior clinical trial data or real-world data (RWD) from administrative claims databases, electronic health records, patient registries, or medical chart abstraction from which individual patient data can be derived.[2] There has been a growing interest in the use of ECA studies and their potential impact on drug development, including the possibility of:

- Expediting drug development and therefore, the availability of novel treatments to patients
- Cost savings compared to a traditional RCT
- Providing stakeholders with valuable information on effectiveness

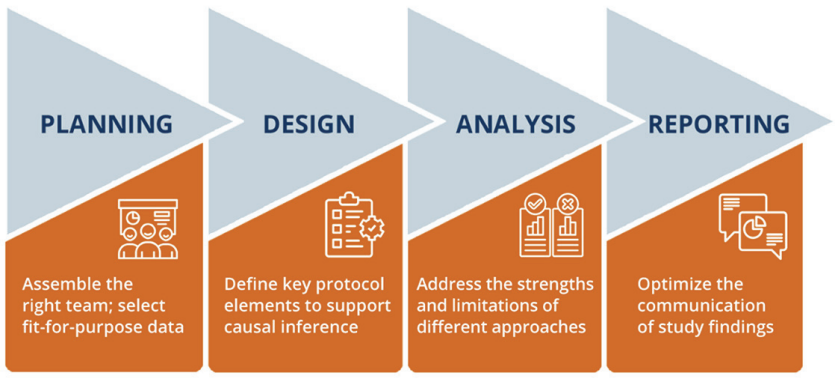
To fulfil the needs of stakeholders, including patients and providers, ECA studies must be carefully planned, designed, executed, and reported in a way that reflects the complexity of the clinical condition and provides the most appropriate results.

Methodologic Considerations

While an ECA can be designed as a benchmark study without a formal comparison to contextualize single-arm trial data, a formal comparative effectiveness study would require more stringent design considerations. The methodologic considerations described below focus on comparative ECA studies.

Broadly speaking, the conduct of an ECA study can be broken down into 4 phases: planning, design, analysis, and reporting (**Figure 1**). Below, we outline important methodologic considerations by phase.

Figure 1. The 4 phases of an external control arm study



Planning: Begin planning early for an ECA Study

The planning stage should ideally begin in parallel to early development and clinical trial design. An ECA study may still be desired in the absence of early planning (eg, the design phase overlapping with a trial read-out) although stakeholders may challenge whether the chosen data sources and specific analyses were conducted to produce a certain finding.

In the planning stage, assembly of the right team and selection of a fit-for-purpose data source are crucial for success. A successful ECA will require input from epidemiologists, biostatisticians, clinicians, and regulatory experts. ECA studies are complex, causal inference studies that require cross-functional stakeholders. A qualified team will appropriately shape the study in the early stages, proactively identify potential criticisms, and validate the study design and data source choices, which is invaluable for efficiency.

The optimal ECA source must be identified by considering the specific research question and selected through a systematic and rigorous fit-for-purpose evaluation (eg, by following published evaluation frameworks).[3,4] Key considerations for data source selection include the ability to apply adapted trial inclusion and exclusion criteria, expected sample size, comparability of the endpoints, validity of the endpoints and other key variables, length of follow-up, availability of prognostic variables, and a thorough understanding of missing data. Even the most rigorous study design and statistical analysis methods cannot overcome data that are not fit-for-purpose.

Design: Prespecification of the ECA study design to support causal inference

Given the lack of randomization and blinding in a single-arm trial, a combination of the target trial and International Conference on Harmonization E9(R1) estimand frameworks[5] can be used to define key protocol elements of the hypothetical RCT that would answer the causal question of interest (the "target trial") and describe how each item can be emulated given the available data.[6,7] Approaching the ECA study design this way helps provide clarity on the causal quantity being estimated and address common threats to internal validity.

Common issues encountered in the design of ECA studies include confounding, selection bias, immortal time bias, and a lack of comparable outcomes (**Table**). These issues should be addressed to the extent possible in the study design and analysis, which need to be prespecified in a study protocol and statistical analysis plan in advance of data analysis. The HARmonized Protocol Template to Enhance Reproducibility (HARPER) template, created by a joint task force between the International Society for Pharmacoepidemiology (ISPE) and ISPOR—The Professional Society for Health Economics and Outcomes Research, provides a helpful framework for communicating study designs in a clear, transparent, and reproduceable manner.[8] It is recommended that the study protocol be registered on a site like Clinicaltrials.gov or the HMA-EMA Catalogues of Real-World Data Sources and Studies in advance of any trial results readouts so that decision makers (eg, regulators, payers) can be confident the trial results had no influence on the chosen methods for the ECA study.[3,9] Finally, engaging regulators early to reach alignment on the anticipated study will help ensure successful submissions.

Table. Common Biases Encountered in External Control Arm Studies

Threat to Validity	Randomized Controlled Trial	Where Problems Can Arise in an ECA	Examples of Mitigation Strategies
Confounding	Randomization breaks the relationship between observed and unobserved patient characteristics and treatment selection/endpoint	In the real world, clinician and patient treatment preferences are influenced by observed patient characteristics; prognostic variables and treatment effect modifiers impact the endpoint	• Clinical knowledge informs selection of prognostic/effect modifier variables to include in statistical analysis • Data source has sufficient capture of prognostic variables • Sample size is large enough to balance observed confounders
Selection bias	The same set of inclusion and exclusion criteria is applied to patients in the experimental and comparator arms	Missing data can interfere with the ability to mimic inclusion and exclusion criteria in the RWD population, leading to systematic differences in the study population between the trial and ECA	• Data source has good capture of variables needed to apply inclusion and exclusion criteria • Appropriate strategies are utilized for handling missing data (eg, multiple imputation)[10]
Immortal Time Bias	Patients in the experimental and comparator arms are screened for eligibility and then outcome capture begins at the time of enrollment	Explicitly or implicitly require a qualification event that occurs after the index date	• Carefully consider how the index date ("time zero") is defined, particularly in the setting of multiple eligible time zeros
Comparability of Outcome	Outcome assessment methodology is standardized and assessments occur at intervals that are typically more frequent than what would be necessitated by clinical care	• Outcome is assessed as needed for clinical care management • Variable or subjective criteria may be used to assess the outcome	• Validation of the outcome of interest • Selection of an outcome that is not time-dependent

ECA indicates external control arm; RWD, real-world data.

Analysis: The strengths and limitations of various statistical approaches should be considered to fit the specific ECA

The methods for analyzing data from externally controlled trials will differ depending upon the research question, choice of data source, and other study-specific factors. Propensity score-based methods are most commonly used, although a variety of causal inference methods exist to address confounding and approximate randomization, such as targeted maximum likelihood estimation, marginal structural models, and G-methods. Assumptions for the chosen analytic plan should be described and those assumptions should be examined through sensitivity analyses and model diagnostics.[11] Specifically, since causal inference methods only account for measured confounding, sensitivity analyses to assess the potential for unmeasured confounding are critical to interpreting results and understanding their validity.

> ECA studies can expedite the development of novel treatments, potentially reduce research costs, and offer needed insights into comparative effectiveness, all of which ultimately benefits patients in need of innovative therapies.

Other analysis considerations include:

- Missing data: Missing data are common in most data sources used for ECAs. Missingness patterns and mechanisms should be assessed and appropriate methods should be incorporated.
- Intercurrent events: These are events that occur after treatment initiation that affect either the interpretation or existence of measurements related to the endpoint. Intercurrent events should be discussed in the design phase and specific methods to handle intercurrent events should be incorporated into the analysis phase.
- Multiple index dates: Research has shown that including all eligible index dates for patients in the ECA leads to the least bias in treatment effect estimates.[12,13] Methods used must account for a patient being included multiple times (eg, a patient meeting eligibility criteria at the initiation of multiple lines of therapy).
- Time-varying confounding: Depending on the treatment effect of interest, important prognostic factors or effect modifiers that change after enrollment may need to be controlled for.

Reporting: Communication of ECA findings to stakeholders and the broader public

Dissemination of the ECA study results to stakeholders and the broader public is an essential step to ensuring that the study can impact decision making and clinical care, as appropriate. Available guidelines, such as the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) and ISPE's Guidelines for Good Pharmacoepidemiology Practices,[14,15] provide helpful guidance for the reporting of observational study findings, including ECA studies. We highlight a few key elements:

- Aim to publish in a peer-reviewed journal
- Be transparent with respect to results reporting (eg, differentiate prespecified versus ad hoc analyses and avoid selective reporting of results from the study[16])
- Disclose all conflicts of interest and sources of study funding
- Discuss study limitations and uncertainty

Takeaways and Future Outlook

ECA studies play a critical role in contextualizing the information learned through single-arm clinical trials. At their best, ECA studies can expedite the development of novel treatments, potentially reduce research costs, and offer needed insights into comparative effectiveness, all of which ultimately benefits patients in need of innovative therapies. Existing methods and data sources often fall short of addressing stakeholder concerns,[17] and we recommend:

(1) Earlier planning and engagement with regulators—in conjunction with clinical trial planning—can increase validity and impact of the ECA study.
(2) Strong partnerships with data providers to identify fit-for-purpose data and increase the reliability and validity of endpoints in RWD to fulfill regulatory, and increasingly HTA body, expectations for outcome validation.
(3) Rigorous methods to ensure valid conclusions, including sensitivity analyses to understand unmeasured confounding.

It is not expected that ECA studies would ever replace RCTs. However, for therapies and conditions where an ECA study is justified, with good planning, design, implementation, and reporting, ECA studies can help fill a knowledge gap and enhance treatment options for patients.

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Distributional Cost-Effectiveness Analysis: A Case Study on Its Potential Prospects in HTA

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Health technology assessment bodies are increasingly interested in health equity and the impact of new medicines on the distribution of health outcomes.

Distributional cost-effectiveness analysis offers a method to measure a medicine's health equity impact alongside traditional cost-effectiveness analysis. The authors illustrate this with a case study in hepatitis C.

A standardized reference case for use of distributional cost-effectiveness analysis in health technology assessment is needed.

Introduction

Interest in distributional cost-effectiveness analysis (DCEA) methods is growing: a DCEA paper focusing on lung cancer published in *Pharmacoeconomics* was the journal's most popular article in 2023.[1] This is not unexpected, as the evaluation of health equity and the influence of novel therapeutics on health outcome distribution are progressively becoming integral elements in the decision-making process of health technology assessments (HTAs). Agencies in the United Kingdom,[2] the United States,[3] and Canada[4] are increasingly assessing health disparities or inequalities.

HTA decision makers typically deliberate the impact that a new medicine may have on health outcomes across different subgroups, such as sex, ethnicity, and socioeconomic status. But the significance of a medicine's impact is often based on qualitative arguments and descriptive statistics.[5-7] In keeping with this approach, deliberation over the extent of health inequity within the target population often involves engaging with key stakeholders, understanding patient experiences, and reviewing evidence indicating that the target population has poorer socioeconomic outcomes than the general population.[6,7] Equity is an important facet to healthcare decision making, yet the process is largely driven by the primary concern of traditional cost-effectiveness analysis (CEA): allocative efficiency.[6,7] The overarching question is whether to implement a particular intervention given the competing demands of a fixed healthcare budget. Traditional CEAs, therefore, attempt to answer a specific question: "What is foregone as a consequence of adopting a new intervention?" In health economics, this is generally what we mean when we talk about "opportunity costs."[8]

While valuable, traditional CEA does not provide a clear, systematic estimation of *how much* impact a new medicine may have on health inequalities across *different* socioeconomic groups.[7] Instead, it assumes that the costs and health benefits of a new medicine are equally distributed across a society's population. Decision makers are therefore unable to analytically judge the potential trade-offs that can arise between efficiency and equity objectives. Simply put, while an intervention may be inefficient for some individuals within society, it could be equitable for others when equity concerns are integrated into the decision problem.[7]

The significance of a medicine's impact is often based on qualitative arguments and descriptive statistics. Equity is an important facet to healthcare decision making, yet the process is largely driven by the primary concern of traditional cost-effectiveness analysis.

So, how could we value health inequalities in a more transparent and reproducible manner? A potential solution is to use DCEA, a type of CEA that provides a quantitative assessment of equity in the *distribution* of costs and effects for different groups of people, as well as information on the efficiency (ie, opportunity cost of a new medicine in terms of its comparative costs and effects).[7] Incorporating an aggregate DCEA, for example, into standard cost-effectiveness models for HTAs provides an approximate distributional breakdown of an intervention's benefits, alongside the conventional CEA.[7]

Applying DCEA in HTA: what could it require?

In addition to conventional CEA outcomes, aggregate DCEA requires data on the distribution of relative inequality between groups for both the target and general populations, and the pre-intervention health inequalities present within the general population.

Relative inequality

A decision maker may be concerned about the health inequality between individuals in terms of biological factors, social factors, economic factors, or a combination thereof.[7] Deciding on how to appropriately delineate health equity is complex and largely driven by the context of the decision problem. Arguably, however, estimating relative health inequalities is largely dependent on the disease and its social determinants.[7] A simple example, which we have used in our case study, is to assume that socioeconomic status is a key determinant of health; this allows us to estimate the distribution of health inequality of different individuals based on Index of Multiple Deprivation (IMD) data.

In England, IMD data comprise 7 domains: income, employment, education, health, crime, barriers to housing and services, and living environment.[9] By grouping individuals or communities based on deprivation, we can generate 5 distinct groups (or quintiles) of relative deprivation, where quintile 1 is the most deprived and quintile 5 is the least deprived.

Pre- and post-interventional health distribution

We also want to calculate the pre- and post-intervention health distribution of the general population.[7] This helps us answer important questions: does the intervention take away health from the general population and give it to the target population (perhaps due to its cost)?; is it net equitable (ie, does everyone benefit?)?; or does it only benefit specific individuals? Pre-intervention health inequalities within the general population are measured using health-adjusted life expectancy (HALE) data.[7] There are various types of HALE measures that estimate health-adjusted life expectancies either from birth or from illness onset.[7] In our case study, we use quality-adjusted life expectancy (QALEs). Simply speaking, a QALE is quality-adjusted survival measured from birth until death.

To estimate the difference in the post- and pre-intervention health distribution across the social groups of interest, we can use metrics such as the Slope Index of Inequality (SII) or Relative Index of Inequality (RII).[7] In our case study, we apply the SII, which is an absolute measure of inequality, estimated, in this case, on the same scale as the HALEs.

> The strength of DCEA is that it will clearly indicate when a new medicine has a negative impact on health inequalities for specific groups of individuals and the whole population.

Equity weighting and post-intervention equity impact

Once we have the necessary aggregate outcomes as well as the proportions of the social equity groups and their HALE data, we can analyze the distributional consequences of costs and benefits for the social groups of interest. From here, equity weights can be applied to each social group to simulate an "equal" distribution of health. We can also estimate the expected impact a medicine may have on health inequality within the target population and the total population.

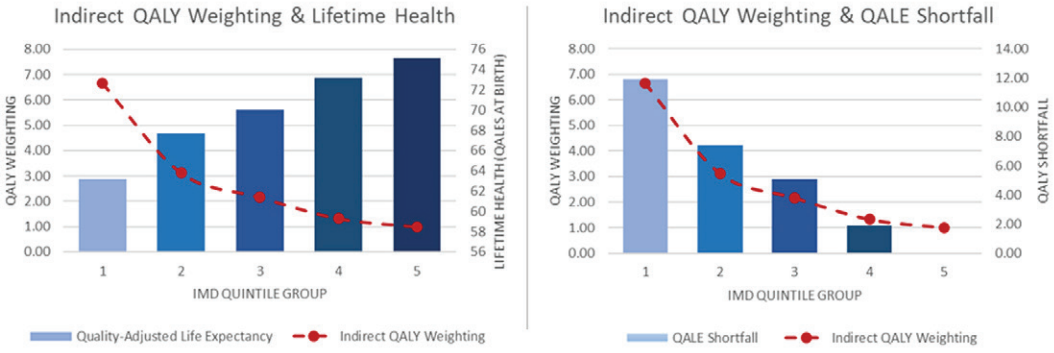
Equity weights can be thought of as the values applied to each social group that move the distribution of health outcomes to a point of equality (ie, a flat health distribution with no quality-adjusted life-year [QALY] shortfall between any of the social groups of interest) (**Figure 1**).[7] In our case study, we apply indirect equity weights calculated using a social welfare function. The magnitude of the weighting is largely determined by an inequality aversion parameter, which determines how much a decision maker "values" reducing health inequalities.[7] Arguably, the higher the decision maker's aversion to inequality, the more they are willing to trade off efficiency objectives in return for reductions in health inequalities. However, it is important to remember that these trade-offs are not a zero-sum game. An intervention can be both efficient and equitable. An intervention can also be efficient for some individuals but inefficient for most, while reducing health inequalities if the health benefits are largely accrued to individuals from poorer socioeconomic groups, for instance. The SII helps us to assess this impact and the associated trade-offs by indicating the magnitude and direction of the change in the pre- and postintervention health of the general population.

A practical case study for HTA

Now that we've explained the concepts associated with DCEA, let's illustrate how to apply them using a tangible case study.

In England, hepatitis C disproportionately affects more deprived socioeconomic groups, with 56% of healthcare resource utilization for the disease attributed to individuals within IMD groups 1 and 2.[10] Because of this, we consider hepatitis C to be a suitable case study for aggregate DCEA in HTA. Aggregate outcomes data are derived from NICE TA507, which

Figure 1. Indirect equity weights and QALY shortfall per IMD group relative to the least deprived IMD group[1]



IMD indicates Index of Multiple Depravation; QALE, quality-adjusted life expectancy; QALY, quality-adjusted life years.
[1]Where quintile 1 is the most deprived and quintile 5 is the least deprived.

assessed Vosevi (sofosbuvir/velpatasvir/voxilaprevir) in direct-acting antiviral drug-naïve chronic patients with hepatitis C in England.[11] The HTA reported incremental QALYs and costs of 1.24 and £20,661 respectively, producing an incremental cost-effectiveness ratio (ICER) of £16,654. For IMD quintile data, we apply Hospital Episode Statistics data to estimate the proportion of patients within each IMD quintile for the target population. For HALEs, we use QALE data for each IMD group derived from an analysis by Love-Koh et al.[12] General population IMD group shares are derived from the same source, based on Hospital Episode Statistics healthcare utilization data distributed by IMD group. For the inequality aversion parameter value, a general rule is to vary this between 0 and 20. We apply an aversion to inequality parameter value of 11, which is an aversion value elicited from the UK general public.[13]

Based on the aversion to inequality parameter value of 11, the indirect equity weights applied to the incremental costs and benefits result in a relatively large (21%) reduction of the ICER reported in NICE TA507, from £16,654 to £13,074. The analysis also indicates that the intervention is net positive for overall population health and, based on the SII, it provides a large, concomitant reduction in health inequality. This is illustrated in **Figure 2** using an equity impact plane, which shows an increase in both net population health and net equity impact. (For further discussion on interpreting the equity impact plane, we refer the reader to Using Cost-Effectiveness Analysis to Address Health Equity Concerns by Cookson et al).[14] But does the ICER *always* improve when considering health inequalities?

The strength of DCEA is that it will clearly indicate when a new medicine has a negative impact on health inequalities for specific groups of individuals and the whole population. If a new medicine increases health inequalities, the net health benefit, net equity impact, and ICER will move in a negative direction. If we assume that patients with hepatitis C in England are mainly distributed within the 2 least deprived IMD groups (groups 4 and 5) (ie, these groups comprise 50% of the hepatitis C population in England), the ICER increases to £20,785 and the net equity impact is negligible. In addition, the National Health Benefit for the most deprived group is negative (ie, the health of the most deprived individuals is *reduced*) (**Figure 3**). Importantly, the SII indicates there is an inequality issue: overall, health inequality is significantly increased.

Developing consistency in equity and appraisal: the value of incorporating aggregate DCEA methods in HTA

DCEA provides a promising method for quantitatively assessing an intervention's health equity impact. Despite several agencies having explicit aims to reduce health inequalities, such as NICE's Principal 9,[15] there is currently no reference case for the appropriate approach to DCEA in HTA submissions. The development of a standardized reference case is desirable because it is important to clearly understand what approach and which data (ie, which social variables, such as ethnicity, gender, or socioeconomic status) are most desired by a decision maker within the context of the decision problem. While there are more comprehensive DCEA methods to consider over and above aggregate DCEA, supplementing current standard CEA submissions with key health inequality metrics that are provided by aggregate DCEA, such as the SII, is a valuable enhancement to standard CEA in HTA.

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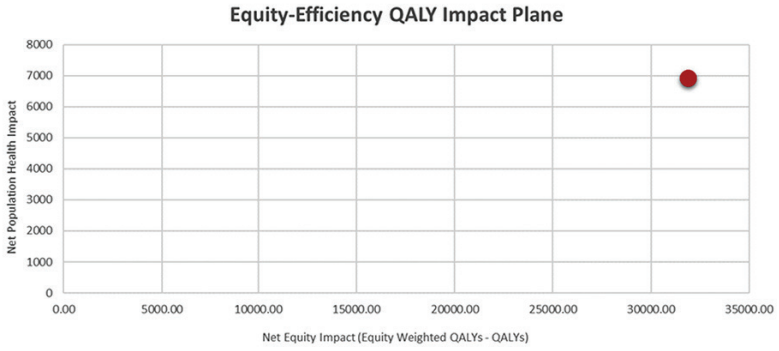
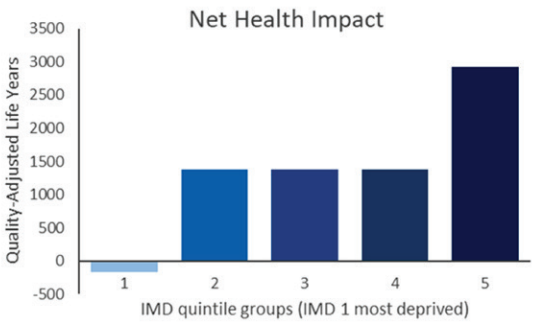
Figure 2. Equity impact plane: Net population health versus net equity impact



QALE, quality-adjusted life expectancy; QALY, quality-adjusted life years.

Figure 3. Net health benefit distribution of case study when most patients with hepatitis C are in the least deprived IMD groups[2]



IMD indicates Index of Multiple Deprivation.
[2]Where quintile 1 is the most deprived and quintile 5 is the least deprived.

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Implementing a Direct-to-Patient Application to Recruit Diverse Patients and Collect Real-World Data: A Case Study

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The Resolve study demonstrated the feasibility of using a direct-to-patient application to recruit diverse patients and collect real-world data. This approach holds promise for collecting granular patient sociodemographic information while protecting privacy in line with the FDA's guidelines.

By combining survey data and claims data, a more comprehensive view of the patient journey can be obtained, allowing for the incorporation of patient's voice into the drug development process and facilitating patient-centered care.

Introduction

Factors such as digital literacy, cultural differences, privacy concerns, data quality, systemic biases, and access to healthcare can affect the enrollment and participation of diverse racial and ethnic minorities, genders, and older adults in clinical research. Marginal sociodemographic groups are often underrepresented or excluded from clinical trials, limiting the generalizability and applicability of the findings to real-world settings and populations, as emphasized by the US Food and Drug Administration (FDA) guidance on enhancing diversity in clinical trials.[1]

The COVID-19 pandemic also highlighted the need for innovative and patient-centric approaches for decentralized and remote clinical trial conduct, while ensuring data integrity and patient engagement.[2] The FDA also noted efforts to make trial participation less burdensome for participants, including the use of online/social media recruitment strategies.

Parexel implemented a direct-to-patient application that leveraged digital and data innovation to recruit patients and collect real-world data (RWD) for a study on oral anticoagulant prophylaxis among patients with cardiovascular diseases. The study, named Resolve, utilized social media to reach out to potential participants across the United States, collected their consent and survey data through a secure platform, and applied a novel tokenization technique to link their data with commercially available claims data. The study aimed to demonstrate the feasibility and value of using a direct-to-patient application to enhance participant engagement, diversity, privacy, real-world data linkage and insights in clinical trials.

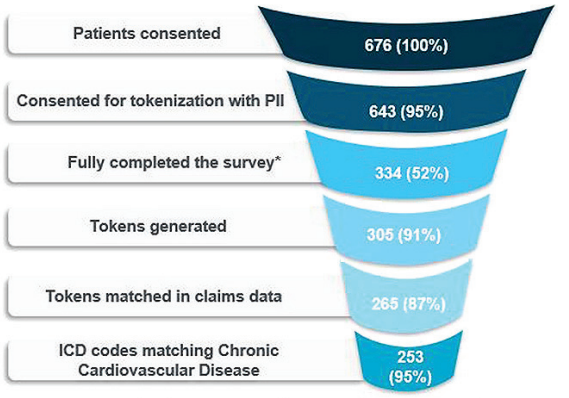
Methods

The Resolve study was conducted between May 2021 and July 2021 and involved multiple technology and data partnerships to ensure a seamless patient experience and data flow. The study protocol and documents were reviewed and approved by an independent institutional review board. The study population consisted of patients aged 40 years and older with cardiovascular diseases who were recruited through social media platforms. The recruitment strategy was designed to target a specific group of patients who are being treated with anticoagulants.

Marginal sociodemographic groups are often under-represented or excluded from clinical trials, limiting the generalizability and applicability of the findings to real-world settings and populations.

The interested patients were directed to a landing page that provided information about the study and the eligibility criteria. The eligible patients were then invited to complete an online informed consent form and a survey questionnaire through a third party's platform. The survey questionnaire collected self-reported data on the patients' demographics, health status, medication use, comorbidities, mental health, and satisfaction with their treatment and care. The survey also asked the patients for their willingness to provide additional consent for tokenization and data linkage. Tokenization is a process of generating unique identifiers (tokens) based on the patients' personally identifiable information, such as name, date of birth, gender, and state. The tokens enable data linkage and facilitate the assessment of patient engagement, recruitment, and feasibility while protecting the patients' privacy and identity.[3] The first 100 patients who consented to tokenization and provided their personally identifiable information were compensated with a $50 gift card. The tokens were generated using the patients' identification data

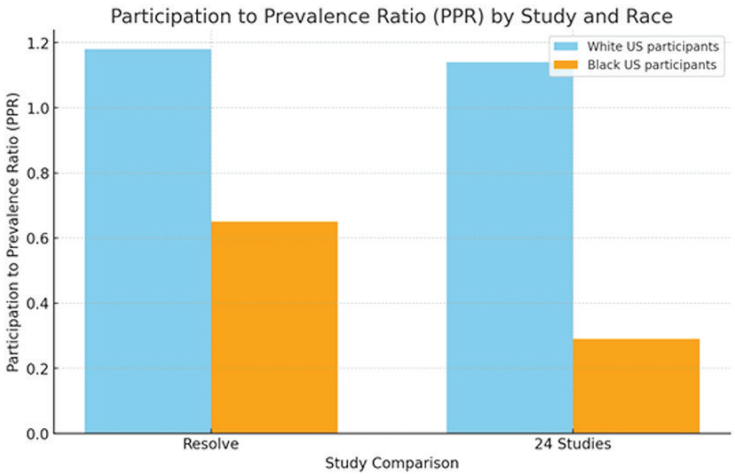
Figure 1. Patient funnel demonstrates the study's success in recruiting specific patients while protecting patients' privacy.



*To fully complete the form at this stage, participants are required to provide their personal data.

ICD indicates International Classification of Diseases; PII, personally identifiable information.

Figure 2. Improved sample diversity in Resolve study relative to existing literature.



and were used to match and link with the patients' data in commercially available claims databases. The claims data provided longitudinal information on the patients' diagnoses, procedures, prescriptions, and healthcare resource utilization. The data linkage enabled a comprehensive evaluation of the patients' journeys, outcomes, and treatment patterns.

Participation of Black US residents in the Resolve study was compared to clinical trials of 24 cardiovascular drugs granted FDA approval (2006-2020).[4] The patient participation to prevalence ratio (PPR) is determined by dividing the percentage of a specific group among trial participants by the percentage of the same group within the disease population.

The data analysis was performed using descriptive statistics, graphical methods, and comparative tests. The treatment pattern of oral anticoagulant medication was analyzed and visualized using an Alluvial plot/Sankey diagram method.

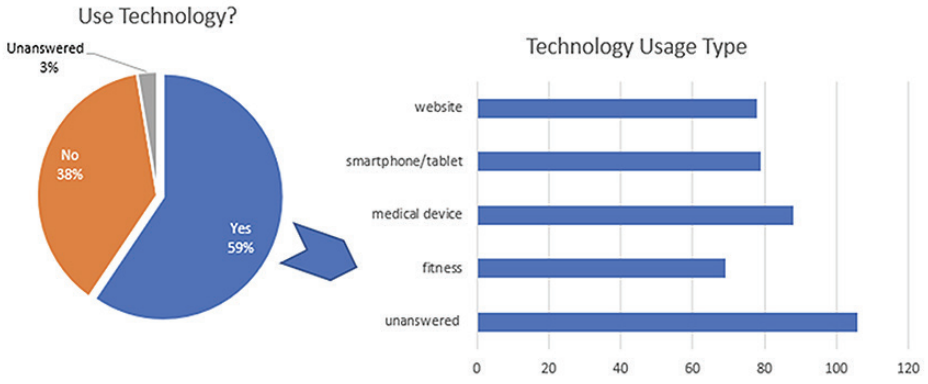
Results

A total of 676 patients in the United States participated in the survey, of which 643 (95%) consented to tokenization and 334 provided their personally identifiable information. Tokens were generated successfully for 305 patients, and 265 patients were linked to tokens in the claims data (**Figure 1**). The demographic breakdown of the participants was as follows: 51% females and 49% males; median age: 66 years (42-85); 85.7% Caucasian; 6.4% Black; 1.5% Latino; 1% Asian American; and 4.5% mixed race. The median annual income among the participants was $27,500 ($2500 to $162,500).

The PPR for Black participants in the Resolve study was 0.65, which was much higher than the PPR of 0.29 in the 24 cardiovascular studies which were the basis of approval for drugs.[4] (**Figure 2**). The Resolve study also exhibited a strong representation of participants of mixed races, Latinos, and Native Americans, as well as women and older adults, compared to previous studies and the overall patients on oral anticoagulants in a commercially available claims database. Throughout the whole study, patients had full control of their data privacy. The study also provided valuable insights into the patients' perceptions, preferences, and experiences with their treatment and care. The survey data revealed that 59.6% of the participants used technology for health and fitness or to monitor health issues, such as smartwatches, fitness trackers, etc. The most common type of technology used was a medical device (33.2%), followed by smartphone/tablet (29.8%), website (29.4%), and fitness tracker (26.0%) (participants could select multiple choices) (**Figure 3**). Most participants (85.5%) reported that they would be interested in participating in future clinical trials.

The claims data enabled a more objective and comprehensive assessment of the patients' clinical outcomes, death records, and comorbidities. The claims data showed that the most common comorbidities among the participants were hypertension (57.0%), diabetes (36.1%), and hyperlipidemia (29.7%), and other symptoms included shortness of breath (41.8%).

Figure 3. Technology use among the Resolve study population.



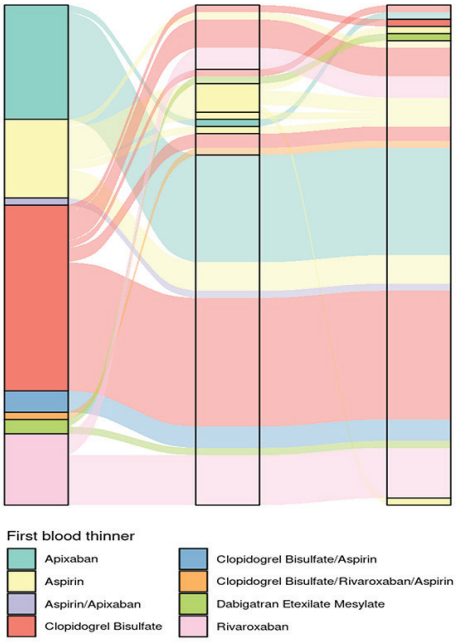
It is important to note that survey data alone do not cover the entire spectrum of diseases and are limited to a predefined set of options. Additionally, the self-reported data represent a specific point in time. In contrast, claims data provide a longitudinal perspective, capturing patient history spanning 9 years before and after the study.

This Sankey diagram visualizes the sequential treatment pattern of oral anticoagulant medications. Each section of a column represents a different medication used, and the lines depict the progression of patient treatment over time (**Figure 4**). The diverse patient sample included in the study seemed to indicate dynamic treatment patterns across the respective options for blood thinners. These findings suggest the need for further research.

Conclusions

The Resolve study demonstrates the feasibility and value of using a direct-to-patient application to recruit diverse patients and collect RWD for clinical trials. The study leveraged social media, digital platforms, and tokenization techniques to reach out to hard-to-reach patient groups, collect their consent and survey data, and link their data with claims data, while ensuring their privacy and identity protection. The study achieved a good racial, gender, and older adult representation compared to prior clinical trials[4-6]; however, additional approaches may be needed to comprehensively include under-represented groups. It provided rich and comprehensive insights into the patients' journeys, outcomes, and treatment patterns.[7] Claims data were consistent with the targeted patient population for the Resolve study, indicating that the majority of the cohort experienced cardiovascular disease issues as well as breathing problems. This aligns with the study period coinciding with the COVID-19 pandemic, during which such health problems were more prevalent. Moreover, the data also revealed mental health issues among the older adult population, which were exacerbated during the pandemic. Furthermore, 3 patients passed away within a year after the survey was conducted: 1 due to suicide and 2 due to COVID-19.

Figure 4. Oral anticoagulant treatment pattern analysis.



> The study underscores the importance of enhancing patient diversity, engaging communities, and employing robust data-linking techniques to optimize interventions and improve patient outcomes.

Although the Resolve study showed a higher PPR rate for Black patients compared to previous trials, it is essential to acknowledge that this still indicates underrepresentation. Adequate representation is typically indicated by PPRs between 0.8 and 1.2, whereas underrepresentation is represented by a PPR below 0.8 and overrepresentation by a PPR above 1.2. Additionally, the PPR for White participants remains relatively high. In future studies, it will be crucial to engage with minority communities to capture a more diverse population. Language assistance can also play a role in facilitating inclusivity and participation.

The study also revealed the patients' high interest and willingness to participate in future clinical trials, especially if they were offered incentives, convenience, and access to new treatments. The detailed race information collected, including the mixed race, was in line with the FDA's new guidance on collecting race and ethnicity data in clinical trials and clinical studies.[8] Finally, the study underscores the importance of enhancing patient diversity, engaging communities, and employing robust data-linking techniques to optimize interventions and improve patient outcomes.

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Advancing Patient Health Through Regulatory-Grade Real-World Evidence Generation

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Real-world evidence (RWE) is increasingly being used to inform decisions regarding the safety and effectiveness of drugs, biologics, and medical devices.

Generating regulatory-grade RWE that can be used successfully to inform regulatory and clinical decisions can be challenging.

To fully unlock RWE's value for patient care, researchers must build on established examples to advance the methodological rigor of RWE generation.

By recognizing the value of RWE, providing consistent guidance, and supporting initiatives to foster its use, health authorities have an important role to play in realizing the full potential of RWE for patients.

Real-world evidence (RWE) generation is at an important inflection point. While real-world data (RWD) have long been used to inform regulatory decisions related to medical product safety, RWE generated from the same underlying data sources is being increasingly used to inform decisions about drug, biologic, and medical device effectiveness.

> Having health authorities recognize the value of RWE, formalize its use through clear guidance, and sponsor initiatives to foster its use to inform regulatory decisions are important steps forward in realizing the full potential of RWD for advancing patient health.

Signaling a heightened consideration for RWE, the US Food and Drug Administration (FDA) released new industry guidance on August 30, 2023[1] and December 21, 2023[2,3] on the use of RWD and RWE for regulatory decisions for drugs and biologics. This adds to the 2017[4] guidance on the use of RWE to support regulatory decision making for medical devices, which was recently updated and circulated for comments on December 19, 2023.[5] The European Medicines Agency (EMA), National Medical Products Association (NMPA) in China, and the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan, among others, are also expanding their adoption of RWE. In addition, health authorities around the world continue to invest in programs to advance the use of RWE for regulatory decisions, such as the FDA's Sentinel and Biologics Effectiveness and Safety (BEST) programs,[6] the National Evaluation System for health Technology (NEST),[7] and the EMA's Data Analysis and Real-World Interrogation Network (DARWIN EU).[8] This collective global effort underscores the growing recognition and adoption of RWE as a valuable tool in shaping informed decision making within the healthcare regulatory landscape.

Having health authorities recognize the value of RWE, formalize its use through clear guidance, and sponsor initiatives to foster its use to inform regulatory decisions are important steps forward in realizing the full potential of RWD for advancing patient health. Pharmaceutical and medical device manufacturers can help further move the needle by applying relevant guidance effectively and consistently and, where applicable, by working through national RWE initiatives to generate the most robust regulatory-grade evidence possible.

Defining regulatory-grade RWE

The first step in facilitating robust RWE generation is establishing a clear, consistent definition of what is meant by *regulatory-grade RWE*. In other words, what requirements must be met to ensure the evidence generated from RWD is sufficiently robust for regulatory decision making? In 2016, as part of the 21st Century Cures Act, the FDA provided guidance on their expectations for RWE,[9] noting that regulatory-grade RWE should be fit-for-purpose (meaning "reliable and relevant") and generated with research that is transparent. Reliability refers to data accuracy, completeness, provenance, and traceability. Relevance refers to data that capture the necessary product exposure, outcome, and covariate information, and that cover sufficient numbers of patients that represent the target population of interest for a given study.[10]

Evolving regulatory applications of RWE

FDA[11] and others[12] have recently documented several examples in which RWE has been used in drug and medical

device regulatory decisions that go beyond assessing product safety. For example, RWE has been used to support drug approval decisions by providing therapeutic context and by developing external control arms for clinical trials.[13] In postapproval settings, significant progress has been made in using RWE to inform label expansions for medical devices. For example, the FDA recently approved Johnson & Johnson's label expansion submission for a cardiac ablation catheter to treat persistent atrial fibrillation based on a comparative RWE study using exclusively electronic health record databases from healthcare systems—a first in the medical device industry.[14] We have also succeeded in using local RWD to confirm that clinical trial results generalize to patients in countries that may not have been included in or were underrepresented in the development program. The resulting evidence was then used to support a transition from conditional to full approval in those countries and to expand indications to pediatric populations when used in combination with trial extrapolation.

> RWE has been used to support drug approval decisions by providing therapeutic context and by developing external control arms for clinical trials

Similarly, health authorities are increasingly seeking data to confirm that the safety and efficacy observed in trials extends to all eligible populations, including underrepresented patient groups. A recent review of clinical trials used for FDA approvals of new molecules and biologics in 2020 found that trial populations comprised only 8% Black and 11% Hispanic individuals, while these individuals represent 13% and 16%, respectively, of the overall US population.[15] By facilitating data relevance (ie, capturing information from a diverse spectrum of patients [age, sex, race/ethnicity, and disease profile]), RWE generated from data sources that include key patient characteristics and outcomes plays an important role in characterizing the safety and benefits of a particular treatment or device across different patient groups to improve health equity.

Considerations for regulatory-grade RWE generation for safety and effectiveness decision making

While the value of RWE throughout the product lifecycle is clear, generating regulatory-grade RWE that can be used successfully to inform regulatory and clinical decisions can be challenging. The real-world environments that give rise to RWD are both what make such data valuable and what creates potential challenges in RWD analysis and use. This is largely due to concerns about data quality, reliability, relevance, and the potential for biases to which observational studies are subject.

We outline several key considerations in the generation and acceptance of regulatory-grade RWE:

1. Engage health authorities early and often. The field of RWE is rapidly evolving and different stakeholders are at different points along their RWE adoption journey. This can result in divergent preferences for the way in which RWE is generated or processes by which RWE is considered, even within the same regulatory agency. By engaging regulators early and maintaining ongoing communication, stakeholders can ensure transparency in and alignment on the approach to RWE generation, while identifying and addressing challenges proactively. For example, the cardiac ablation catheter approval mentioned earlier was based on a test case study conducted through NEST, which is a public-private partnership supported by the FDA and in which members of the FDA are actively involved. This collaborative approach helped foster a deeper understanding of RWE, but also cultivated a foundation of trust and transparency to reinforce the value of RWE in regulatory decisions.

2. Design the RWE study like a randomized trial. While using reliable and relevant data is necessary for generation of regulatory-grade RWE, it alone is not always sufficient for producing robust evidence. Confounding, time-related biases, and inappropriate adjustment for post-baseline variables are common sources of bias in real-world studies of medical product outcomes. Designing an observational study to emulate a target trial that would answer the question of interest can increase the probability that the evidence generated is reliable.[16] For example, clearly specifying eligibility criteria, treatment strategies, outcome(s), follow-up, causal contrast(s) of interest, analysis plan, and time zero (ie, baseline) can help reduce potential biases in observational studies.[17]

> The field of RWE is rapidly evolving and different stakeholders are at different points along their RWE adoption journey. This can result in divergent preferences for the way RWE is generated or considered, even within the same regulatory agency.

3. Prioritize rigorous, empirical diagnostics. Even when using fit-for-purpose data and employing a study design that emulates a randomized trial, some questions of regulatory importance cannot be reliably addressed using RWD. The reasons for which RWD may be insufficient for a particular question are sometimes apparent. The tenability of assumptions required for valid causal inference may be less obvious, but can be informed by empirical diagnostics, which are checks that can be performed on study databases and cohorts to assess whether an estimated treatment effect is likely to be valid. For example, one can assess whether sufficient balance in baseline or pretreatment patient characteristics exists between treatment groups to enable a valid comparison. Negative control outcomes can be used to assess the potential for residual confounding beyond observed balance in measured covariates.[18] These and other diagnostics, including those that can be used to inform data fitness-for-purpose determinations, can be systematically deployed prior to estimating a treatment effect. This stepwise approach helps ensure that

only evidence that passes diagnostics is generated, and results that are likely to be subject to substantial confounding or other biases—therefore inaccurate and misleading—are avoided.

4. Evaluate the robustness of the evidence. Certain prespecified analyses can be helpful for confirming that generated evidence is indeed robust, consistent, and generalizable. In their framework for RWE programs, the FDA indicated a focus on prespecifying sensitivity analyses for RWE studies for effectiveness.[19] Conducting such analyses across multiple data sources provides an opportunity to assess for unanticipated or otherwise undetected biases or important differences in treatment effect that vary across patient populations.[20] Quantitative bias analysis can also be used to assess the impact of potential residual biases, including bias due to confounding and outcome misclassification.[21]

> Accelerating innovation and unlocking the full value of RWE to advance patient care will require health authorities to further consider the evolving evidence needs of today's healthcare landscape and their implications on safety and effectiveness decision-making standards.

Unlocking the full value of RWE for patients

Accelerating innovation and unlocking the full value of RWE to advance patient care will require researchers to build on now established examples to continue to advance the methodological rigor of RWE generation. It will also require health authorities to further consider the evolving evidence needs of today's healthcare landscape and their implications on safety and effectiveness decision-making standards.

Moreover, it is important to remember that robust RWE is not only beneficial to health authorities, medical product innovators, and manufacturers, and that the considerations outlined here to support generation of regulatory-grade RWE are not only applicable for regulatory decision making. The value of robust evidence is critical across all types of healthcare decisions, including health technology assessments and payer decisions, clinical guidelines to inform treatment choices, and disease epidemiology to support health policy.

> We can create a world in which RWE produces a comprehensive understanding of disease and the effects of medical products used in routine clinical practice to enable more confident and informed benefit-risk decision making by all stakeholders.

Through a concerted effort across the healthcare ecosystem, we can create a world in which RWE produces a comprehensive understanding of disease and the effects of medical products used in routine clinical practice to enable more confident and informed benefit-risk decision making by all stakeholders.

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Improving Patient Access to Medicines Targeting Early Stage Cancers in Europe

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Development of medicines in early stage cancers has increased significantly in recent years and is expected to continue increasing along with expected clinical and economic benefits for patients and healthcare systems.

Despite that, there remain important barriers to patient access to medicines in early stage cancers in Europe, both before reimbursement decision making and after reimbursement along the patient care pathway.

In the context of the current reforms of the European health technology assessment (HTA) landscape (eg, Joint Clinical Assessment), consideration of how HTA bodies can properly recognize the value of medicines targeting early stage cancers is important.

Introduction

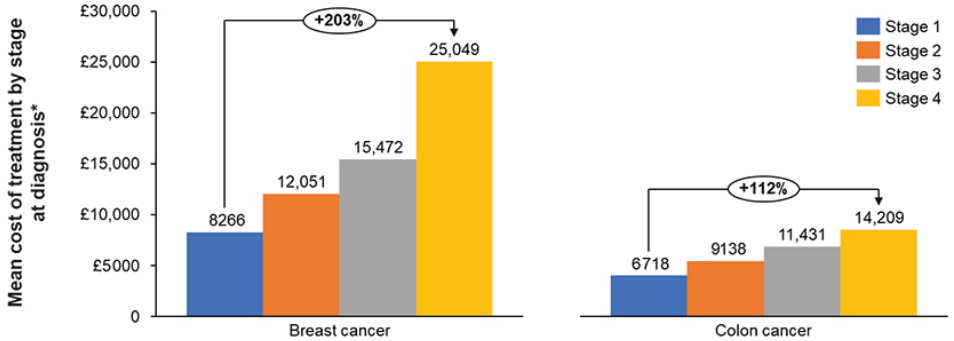
Timely diagnosis and prompt surgical treatment in early stages of cancer can enhance patient outcomes. Yet long-term studies indicate a higher risk of recurrence in some patients without the aid of (neo)adjuvant therapies.[1] Development of medicines targeting early stage cancers (ESC) has increased in recent years and is expected to continue increasing, bringing significant benefits for patients and healthcare systems. However, there remain important barriers to patient access, including difficulties in recognizing the long-term benefits of those medicines or ineligibility because of delayed diagnosis and disease progression.

This analysis focuses on European countries and aims to provide a comprehensive overview of the benefits of innovative medicines for ESC, assess current challenges to patient access to such treatments, and identify key policy solutions to overcome those challenges.

Clinical and economic benefits of treating cancer early

Innovative medicines targeting ESC are associated with many clinical benefits and could improve quality of life through improving cure rates and decreasing/reducing the risk of relapse and cancer-related symptoms. In early stage non-small cell lung cancer (NSCLC), perioperative immune checkpoint inhibitor therapy has demonstrated a significant improvement in 24-month event-free survival rates from 40.6% to 62.4%.[2] Similarly, in early stage triple-negative breast cancer (TNBC), combining immune checkpoint inhibitor therapy with chemotherapy has been shown to improve event-free survival at 36 months from 76.8% to 84.5% compared to chemotherapy alone.[3] These therapies also improve surgical outcomes by increasing the success rate of tumor removal and reducing post-surgery complications. Furthermore, they have the potential to alleviate the mental health burden on patients by reducing the risk of tumor recurrence.[4] Certain ESC-targeted therapies may be considered cost-effective or even cost-saving in the long-term. By aiming to prevent cancer recurrence, these medicines help reduce the need for higher-cost late-line treatments, resulting in overall cost savings. Studies in the United Kingdom have shown that treatment costs in breast, colorectal, and prostate cancers increase with disease stage and conclude that earlier stage diagnosis is associated with larger cost savings (**Figure 1**).[5] In Germany, mean direct medical costs associated with breast cancer are twice as expensive for patients with stage IV compared to stage I.[6] Another study shows that introducing immune checkpoint inhibitors

Figure 1: Mean overall treatment costs per patient by stage in breast and colon cancers in the United Kingdom (adapted from Wills L, et al).[5]



*Treatment costs refer to surgery, radiotherapy, chemotherapy, targeted therapy, immunotherapy and endocrine therapy, but does not include diagnostic tests, hospital admissions, critical care unit beds, and supportive medicines.

in early stage melanoma, renal cell carcinoma, and TNBC helps avoid about 30% of active treatments in the metastatic setting over 10 years. Finally, use of immune checkpoint inhibitors in ESC have been demonstrated to prevent the need for neoadjuvant chemotherapy.[7]

> Development of medicines targeting early stage cancers has increased in recent years and is expected to continue increasing, bringing significant benefits for patients and healthcare systems.

In addition to cancer care cost savings, medicines targeting ESC bring impactful economic advantages as they lead to a decreased need for non-oncology treatments and reduced economic costs associated with lost productivity. Psychological disorders affect up to 25% of cancer patients and double annual healthcare costs for those affected. Studies also show the psychological burden on families (eg, partners and children of patients with cervical cancer have 30-40% increased risk of mental disorders). Medicines targeting ESC may deliver psychological benefits to patients and their families by reducing anxiety and psychological stress caused by the risk of relapses, therefore improving quality of life and reducing nononcology treatment costs.[8]

With early diagnosis of cancer being more likely to impact younger patients in their working years, and with increased incidence of cancer cases in younger age groups, earlier treatment allows them to resume work earlier. Unemployment doubles from 2 years after endometrial or cervical cancer diagnosis and onwards. Productivity loss also impacts caregivers and families, as about 15% of caregivers of lung cancer and breast cancer patients left the workforce post-diagnosis.[9]

Challenges to patient access to medicines targeting ESC

While the clinical and economic benefits of medicines targeting ESC are increasingly acknowledged, patient access to those treatments remains more limited. Comparison of reimbursement rates for medicines targeting ESC compared to all cancer treatments in Europe shows that medicines targeting ESC face substantial barriers in achieving reimbursement, with an average reimbursement rate of 62% for medicines targeting ESC in Europe, compared to 77% for all cancer medicines (**Figure 2**). Studies show that high challenges are faced by both neoadjuvant and adjuvant treatments.[10]

Despite the value drivers of treating ESC, challenges demonstrating cost-effectiveness are common, since HTA bodies and payers have traditionally considered median overall survival (OS) to be the "gold standard" clinical endpoint in oncology, but there are several issues affecting its use in novel treatments of ESC. Instead, disease-relevant endpoints are typically used and recognized as valuable by clinicians as they can better measure clinical and quality-of-life benefit in slow-progressing cancers, deal with the issue of confounding faced by OS for multiple consecutive lines of treatment, better capture the patient's perspective, and shorten clinical trial durations.

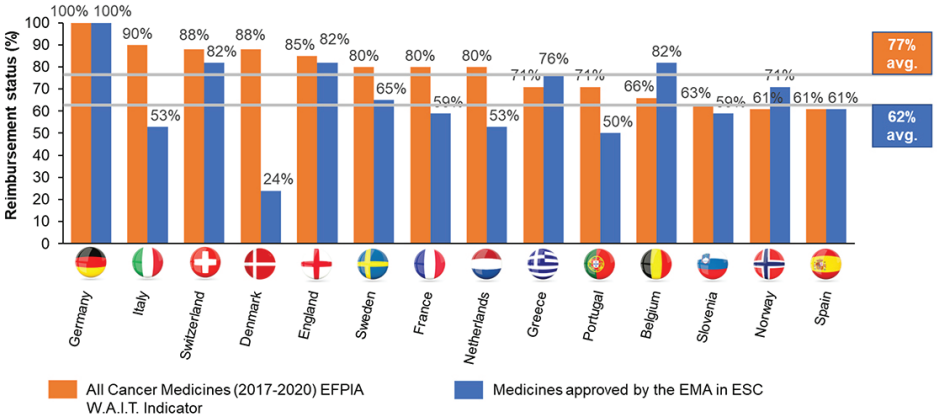
> HTA bodies and payers have traditionally considered median overall survival to be the "gold standard" clinical endpoint in oncology, but there are several issues affecting its use in novel treatments of early stage cancers.

However, disease-relevant endpoints, and especially quality-of-life endpoints, are not universally accepted and views vary between stakeholder groups on the value of disease-relevant endpoints (eg, EUNetHTA21 guidelines state that while morbidity and health-related quality-of-life impact are valued, they are considered below mortality in the outcomes hierarchy).

In addition, affordability and underfunding of healthcare systems constitute other barriers to patient access to ESC. This manifests itself by deprioritization of treatments for ESC due to uncertainty around patient population size or long-term effectiveness. Consistency across countries on the type of data required supported by robust HTA methodological guidelines to be able to assess the long-term benefits of medicines targeting ESC (eg, long-term impact on patient survival, and local and distant metastasis-free survival), should be followed in practice.

Once a medicine is reimbursed, other challenges can also hinder the use of medicines targeting ESC. Disease awareness from primary care

Figure 2: Reimbursement status of medicines approved for ESC indications by the EMA between 2015 and 2019 in ESC versus all cancer medicines across European countries (Source: CRA analysis of publicly available data).



EFPIA indicates European Federation of Pharmaceutical Industries and Associations; EMA, European Medicines Agency; ESC, early stage cancer.

practitioners, limited availability of screening programs to detect early disease, and low patient knowledge of these methods contribute to delayed diagnoses and cancer progression to later stages, leading to potential ineligibility for ESC treatments. Moreover, European/national guidelines recommending the use of medicines targeting ESC may not be updated frequently enough and/or widely adopted. Finally, fragmented healthcare systems and/or limited healthcare capacity can be a key issue (eg, patients not properly tracked in the system or not treated at the right time, low adoption of digitalized healthcare systems).

Overall survival is considered to be the "gold standard" clinical endpoint in oncology because of its relatively wide recognition and straightforward application. However, the literature identifies several issues inherently incurred to the use of overall survival as an efficacy measure for novel medicines in ESC:

(1) Due to the greater longevity of patients with ESC, lengthier clinical trials would be required to measure the impact of a new therapy on overall survival;

(2) Measurement of overall survival carries a risk of confounding because of subsequent relapses and complex regimens with multiple lines of treatment in later cancer stages, making it hard to assign the clinical benefit to a specific treatment;

(3) Overall survival is not able to capture patient's perspective on aspects relating to quality of life (eg, pain relief, symptom control, etc)

Given these issues, the use of "non-overall survival" or "disease-relevant endpoints" has been documented as a more suitable approach in situations where improvement in overall survival is challenging to measure. Disease-relevant endpoints can refer to a physiological measure, laboratory test result, imaging result, or other replacement endpoint capturing the causal pathway through which the disease process affects patient-centered outcomes. "Event-related" endpoints such as disease-free survival, progression-free survival, and event-free survival are some of the most frequently used disease-relevant endpoints in the adjuvant or nonresection setting for medicines in ESC.

Solutions to improve patient access to medicines targeting ESC

A range of potential solutions is required to address multifactorial barriers to access to medicines targeting ESC (**Figure 3**). The systematic use of early dialog between manufacturers and HTA bodies/payers on disease-relevant endpoint evidence requirements is important to improve their acceptance and enabling timely patient access to treatments targeting ESC. Manufacturers and trade associations can work with regulators and payers and engage with clinicians and patient advocacy groups, to discuss approaches to reduce uncertainty related to clinical evidence and increase acceptance of disease-relevant endpoints. While the upcoming Joint Clinical Assessment (JCA) established by the EU HTA regulation may represent a first step toward greater harmonization of the type of evidence required, national appraisal and value assessment would remain at each country level. As there can be considerable variability in terms of endpoints acceptance and consequent patient access outcomes across European countries, there is an opportunity for local key opinion leaders to show their endorsement of disease-relevant endpoints in demonstrating the benefits of medicines in ESC.

Where budgetary uncertainties linked to patient population size are a major concern for payers, volume-based contracting agreements (eg, price per volume contracting) or bundle payment models for both testing and treatment may be leveraged to alleviate concerns (eg, in France or Germany). It can also be useful for patient advocacy groups to support inclusion of ESC in national cancer control plans.

When looking to improve use of medicines targeting ESC, higher investment in screening and testing should first be considered to ensure as many cancers as possible are detected in early stages. This could be driven by the development and consideration of evidence of the clinical and economic benefits of early screening and testing. Uptake of screening may be improved through increased patient awareness, while involvement of physicians and patient advocacy groups in discussions supporting guidelines implementation could increase homogenization of higher quality-controlled practices in the real world and reduction of inequal access.

Figure 3: Summary of key policy solutions to alleviate patient access barriers to medicines targeting ESC.

ESC indicates early stage cancer; EU, European Union; HTA, health technology assessment.

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Q&A

Interview With Peter Arlett: Head of Data Analytics and Methods, European Medicines Agency

The European Medicines Agency's Peter Arlett looks back on 2 years of the Accelerating Clinical Trials in the European Union (ACT EU) initiative which aims to improve the environment for clinical trials in the EU by transforming how trials are initiated, designed, and run. In conversation following DIA Europe 2024 in Brussels, Arlett also highlights the impact of the DARWIN EU real-world evidence (RWE) program in its 2 years of existence as more data partners are added and studies conducted.

"We are in the business of excellent clinical evidence. EMA wants to partner with stakeholders, to drive up the quality of evidence that supports the decisions of regulators, HTA bodies, and payers."

– Peter Arlett

Photo Credit: European Medicines Agency

PharmaBoardroom: Two years on from its implementation, what impact has ACT EU had on invigorating the EU clinical research environment?
Peter Arlett: After 2 years, we have made great progress towards the broad goal of ACT EU: better and more impactful clinical trials in Europe.

Firstly, we have brought the complex web of regulatory actors at both the member state and European level together. We have also launched a Multistakeholder Platform Advisory Board which brings together about 50 different stakeholders from patients to academia and commercial sponsors. There, they can discuss their priorities for invigorating the research environment and making clinical trials more impactful more generally.

This year is the last in the transition to the Clinical Trials Regulation (CTR) (2022-2025), meaning we are almost at the finish line of the transition. Any change has the potential to be painful, with people needing to be trained to work differently, but the progress has been impressive.

The Clinical Trial Information System (CTIS) that was launched in 2022 had challenges at the beginning but is now working much better, with high volumes of clinical trial applications being processed through it. A big advantage of this system is that sponsors only need to submit a single application to the IT system for a clinical trial that could potentially run across every EU member state.

Additionally, also under the auspices of ACT EU, we have rolled out some important guidelines on decentralized clinical trials. Prior to this paper, released last year, regulators had not given clear guidance on managing the benefits of decentralized trials (such as accessibility for patients) with its challenges (such as maintaining data integrity and less face-to-face patient supervision).

Finally, we have made major progress in bringing together scientific advice from both the European and national levels on research and development program design. Eventually, this will mean that sponsors will receive responses to requests for scientific advice from both EMA's Committee for Medicinal Products for Human Use and the Heads of Medicines Agencies (HMA) Clinical Trials Coordination Group concurrently. We launched some combined advice pilots under the ACT EU umbrella in May this year, which represent an important and concrete step towards decomplexifying clinical trials.

PB: What type of trial sponsors stand to benefit most from these regulatory upgrades?
PA: Commercial sponsors, as historically, there has been a significant skew towards these sponsors in multinational clinical trials, and this remains today. Having said that, we are going to be launching various support programs and initiatives to support noncommercial clinical trials. This is vitally important, as was shown in the COVID-19 pandemic where, apart from vaccine studies, most of the other studies (therapeutics and repurposing) were done by academia. We need to continue to support academia to ensure that their trials are bigger and more impactful going forward.

> Bringing together ethics bodies, which tend to sit at a national level, will really speed up the rollout of big multinational clinical trials and reduce the time needed to consult with multiple national level stakeholders.

PB: By the end of January 2025, any ongoing trials under the previous legislation, the Clinical Trials Directive, will need to be transitioned to CTIS to follow the Clinical Trials Regulation regime. Given the initial teething problems that CTIS faced, how ready are stakeholders across the European ecosystem for this impending cut-off?
PA: There is a maximum of 5000 ongoing trials under the Clinical Trials Directive which will need to be transitioned to CTIS. We have already authorized 900 of these through CTIS and are ready to authorize the remainder. I would like to issue a call to arms for sponsors to get those applications into CTIS, because the EU Regulatory Network is ready to receive them. We have published guidance and an expedited procedure is in place, but processing takes time. It can take up to 3 months to process the applications, so if they all come in in November and December 2024, things will get very tight.

PB: Have clinical trial numbers in Europe risen since ACT EU was passed?
PA: There have been approximately 2500 clinical trial applications since the launch of CTIS in January 2022 and we are authorizing about 300 clinical trials per month. These numbers have remained largely the same over the past decade, with the COVID-19 period complicating the analysis for a couple of years. The problem statement is not, as has been reported in some quarters, that European clinical trials are declining. It is that they are not growing, as they have been in the United States, for example. The EU has extremely strong hospitals, hospital networks, and academia: all the ingredients needed for conducting outstanding clinical trials. Moreover, historically, Europe has been the engine room of global clinical trials, but we haven't seen the growth. This means that we need to foster this growth in clinical trial numbers, size, and level of innovation.

Some big positives beyond trial numbers are already apparent. Primarily, EMA internal analysis shows that the number of member states per commercial multinational clinical trial is higher under the Clinical Trials Regulation than it was under the Clinical Trials Directive. This is almost certainly because under the Clinical Trials Regulation sponsors can apply to multiple member states with one application. This holds a lot of promise in terms of more, larger multinational clinical trials, whether in 2 or 27 member states.

PB: Does EMA have any preference in terms of the kinds of clinical trials it is hoping to attract to Europe?
PA: Different stakeholders will have different answers to this question. A patient association representing patients with a particular rare disease would ask for really well-designed clinical trials around that rare disease. The oncology community might want a big clinical trial focused on optimizing the various cancer medicines that are already authorized. A pharma company might want rapid recruitment for a phase II or III trial of their new investigative medicine.

From EMA's perspective, we want to put in place the ingredients to support whatever type of clinical trial a sponsor wants. This includes those utilizing innovative methods or decentralized elements, with the overall goal of collectively invigorating the clinical research environment in Europe.

PB: The COVID experience continues to loom large for regulators across the world and ACT EU includes a focus on clinical trials in health emergencies. To what extent is Europe better prepared today to tackle the next pandemic in terms of fast, efficient, cross-border clinical trials than it was in 2020?
PA: We've come a long way. In terms of clinical trials during COVID, we were too slow and too small in Europe. None of the clinical trials that led to the authorization of the COVID vaccines rolled out in 2020 and 2021 were held in the EU, which was telling. Additionally, there were many clinical trials registered in Europe for repurposing therapeutics but, in general, they were too small to be impactful. Moreover, the big clinical trials that were planned took an exceptionally long time to get off the ground.

To address this, we have rolled out several initiatives. In June 2023, EMA cohosted a highly successful public workshop with the European Commission's DG Research and DG Sante. The morning session focused on regulatory hurdles and what we can do to improve and speed up the authorization of clinical trials, while the afternoon looked at infrastructure and funding for fighting public health emergencies.

We're not at our destination yet but we've made significant progress. One example is the Guidance on Regulatory Flexibility for Clinical Trial Applications in Public Emergencies. This guidance minimizes the number of documents that need to be submitted in a health emergency, ensures we have an agile scientific advice offering service, and reinforces the role of EMA's Emergency Task Force which brings together regulators with ethics bodies and other stakeholders to ensure that the advice is easily implemented. Bringing together ethics bodies, which tend to sit at a national level, will really speed up the rollout of big multinational clinical trials and reduce the time needed to consult with multiple national level stakeholders. While the ultimate responsibility for ethics decisions will remain at a national level, this is clearly a concrete step forward.

Finally, upgrades on the clinical trial infrastructure and funding side have been embraced at the Commission level, actively supported by EMA. There are interesting discussions ongoing around establishing "ever warm" clinical trial networks for better preparedness and response to public health emergencies. The European Commission is also talking about creating a coordination mechanism so that with advice from EMA, they can pick products to be subject of clinical trials and gain direct funding fast in the event of an emerging public health emergency. All in all, we still have headroom for improvement, but step by step, we are working through the problems that exist to ensure that we are faster in future.

PB: When we spoke to EMA Executive Director Emer Cooke last year, she told us that while the DARWIN EU RWE program only completed 4 studies in 2022, there were plans for between 10 to 15 in 2023, and around 150 per year from 2025. Have these milestones been met and what have been the challenges faced in scaling up this initiative?
PA: DARWIN EU promises to be a great success. It is growing and delivering clinical evidence via real-world data studies. In terms of data partners, we had 10 in the first year, we now have 20, with plans for 30 by the end of 2024 and 40 by the end of 2025. The current 20 data partners represent 130 million active patients who are continually contributing data, making this a massive and powerful system already.

So far, we have completed 14 studies, with 11 ongoing and the potential to initiate up to 70 additional studies this year, which is in line with our planning. This could vary if we focus on more complicated studies. From 2025, we are contracted to a ceiling of 140 studies, which is an absolute game changer. As far as I'm aware, no other organization in the world has ever done RWE studies in those kinds of numbers before.

We are going to be able to do this thanks to a few secret ingredients. The first is the use of a common data model. The data partners and datasets we are onboarding are converted into a common structure with mapped terminologies, meaning that computer scripts can be run through the entire dataset despite the original data source being in different formats. Researchers can then upscale in terms of the number of data sources rather quickly. For example, this means that if a study happened last year using a particular protocol with 3 data sources, this same study could potentially be replicated this year within a matter of weeks through another 10 data sources.

Currently, we are looking at a whole array of different types of studies and questions. We can look at disease epidemiology—understanding who gets a particular disease, their age, gender distribution, their symptoms or mortality, how they are treated, the pathway in terms of therapeutics, and the natural population with a disease compared to the clinical trial population. This allows us to understand the external validity and relevance of the clinical trial results to the general population or the general population with that disease.

> There is a huge interest from the industry in RWE effectiveness studies, but from a scientific point of view, this is the area where we need to go most cautiously given that it is less well-established than the drug safety area.

We can also do causality studies: looking at associations between particular medical events and exposure to medicines. This is very well established in the drug safety area and has been done for over 30 years but is still relatively new in terms of efficacy and effectiveness. For example, there were some promising vaccine effectiveness studies using DARWIN conducted during COVID because high levels of testing meant that there were a lot of records of infection. Naturally, there is a huge interest from the industry in RWE effectiveness studies, but from a scientific point of view, this is the area where we need to go most cautiously given that it is less well-established than the drug safety area.

PB: How would you define a "complicated" RWE study?
PA: Firstly, complexity can be defined by whether something has been done before. For example, if we have done a study of the natural history of multiple myeloma, written the protocol, identified data sources, and learned from doing, then repeating a study like that would be quite straightforward. Within DARWIN we call these "routine repeat studies." Another example was one of the studies we completed last year, looking at drug utilization of antibiotics. This is particularly relevant in monitoring for antimicrobial resistance as these were antibiotics on the World Health Organization's watch list of antibiotics for concern. We were able to look at how the antibiotics are being prescribed and what they have been prescribed for. Now we have done that and established protocols, as we onboard new data partners, potentially every year, we can repeat that study and look at trends in prescribing over time. This is interesting from both a public health policy and antimicrobial resistance prevention perspective.

An additional complexity element is simply the methodological complexity of the question. Looking at the example of efficacy and effectiveness, one of the reasons that we rely on randomized controlled trials is that the randomization process deals with bias which is the core strength of the methodology. For real-world data studies there is no randomization. This means that for effectiveness studies very granular data on the patient and treatment is needed, all of which must be balanced

to address potential bias, creating greater complexity. On the other hand, descriptive observational studies using real-world data, for example, in disease epidemiology or drug utilization, tend to be much more straightforward.

PB: What kinds of organizations and institutions have signed up as data partners for DARWIN EU thus far?
PA: Institutions from 13 different countries have signed up thus far. They are bringing a mixture of general practitioner datasets, hospital data sets, and a couple of registries. For example, we now have The Netherlands Cancer Registry on board, as well as their integrated primary care information dataset.

An exciting newly onboarded data partner is the French Health Data Hub, which has access to the entire insurance dataset of France. This is going to be an enormously important source of data going forward as, certainly outside of France, it has been little researched. DARWIN EU's ability to research this data will open up tons of opportunities for questions about medicines, regulation, and public health policy.

> We decided that science and public health should be driving our decisions.

The Nordic health registries—particularly those of Norway, Denmark, and Finland—are of great quality. While the individual countries' populations are not as big as those of countries like France, if we are able to do studies across the different registries, then we will be able to generate extraordinarily rich and informative evidence. This has already been shown through the COVID-19 vaccine effectiveness studies which included the Nordic health registries, making this an extremely exciting region from a data-sourcing perspective.

PB: I notice that the United Kingdom is also a partner, even post-Brexit. Is that unusual?
PA: Some of the UK's data sources are truly excellent, and we decided that science and public health should be driving our decisions. We therefore talk about "European" rather than "EU" data sources. The inclusion of the United Kingdom has brought scientific benefits.

The UK's Clinical Practice Research Datalink, run by the Medicines and Healthcare Products Regulatory Agency, is of excellent quality and probably the most studied electronic health record dataset in the world. We have also recently onboarded the UK Biobank which will allow us to link genomics data to clinical records and clinical outcomes, which is quite exciting and cutting-edge.

PB: How do you hope to expand the DARWIN EU network even further, both in terms of geography and types of data partners?
PA: On the DARWIN EU website, there is an open call for data partners, where interested institutions can send in some basic information about their dataset. Another important evolution has been the very recent launch of an HMA/EMA catalog of real-world data sources (https://catalogues.ema.europa.eu/). This is a big deal and is an all-singing-all-dancing catalog which takes fingerprints of the datasets and allows data to be discoverable. This catalog has only just been launched and there are only 200 or so datasets on there right now, but over time we will be reaching out to different stakeholders with the aim of including thousands of datasets. That means that the data will then be discoverable (some refer to "findable"), allowing researchers to look at certain metadata around aspects of quality, representativeness, and so on. That is also helpful to us as EMA in selecting future data partners.

Ultimately, we are making choices on data partners based on the questions we get. For example, around 50% of all new marketing authorization applications coming through EMA are in oncology, meaning that we want to make sure we have good data on patients with cancer and cancer treatments. Another area where we are getting a lot of questions is pediatric use. EMA's Paediatric Committee has a difficult job of deciding which products developed for adults should also be developed in children, and if so what the clinical trials or evidence package should look like. Therefore, that might drive a preference to onboard datasets that include pediatric data, ultimately helping the Paediatric Committee better answer these challenging questions.

PB: Do you have a final message for PharmaBoardroom's industry-focused audience on behalf of EMA?
PA: We are in the business of excellent clinical evidence. EMA wants to partner with stakeholders, including those from industry, to drive up the quality of evidence that supports the decisions of regulators, HTA bodies, and payers. Bigger, better, and more impactful clinical trials are one part of this while enabling the use and establishing the value of RWE is another. That is our vision, and we are on track to achieve it.

The industry should work with us to pursue ever better evidence on medicines. This will potentially lead to earlier authorization of medicines and optimization of their use. The industry will benefit, but most importantly public health and patients will too.

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