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VALUE & OUTCOMES SPOTLIGHT

A magazine for the global HEOR community.

Measuring THE PROMISE of Obesity Drugs

ISPOR

Improving healthcare decisions

VALUE & OUTCOMES
SPOTLIGHT

JANUARY/FEBRUARY 2024
VOL. 10, NO. 1

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

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Weighing in on the Obesity Epidemic

Obesity, recognized as a complex health condition, has a long and multifaceted history. In the last century, obesity gained prominence as a global health concern. Industrialization, urbanization, and changes in lifestyle contributed to rising obesity rates. The medicalization of obesity emerged, with researchers exploring its genetic, hormonal, and metabolic aspects. Today, obesity remains a critical public health issue, necessitating comprehensive strategies for prevention and management. According to the World Health Organization (WHO), obesity rates worldwide have nearly tripled since 1975. The United States also faces significant challenges with obesity. In the early 1960s, approximately 13% of the US population was obese according to Centers for Disease Control, but this rose to 41.9% by 2020.

> According to the WHO, obesity is a major risk factor for heart disease, stroke, high blood pressure, diabetes, musculoskeletal disorders, some cancers, and more.

Obesity is recognized as a chronic disease by organizations like the American Medical Association, which emphasizes its impact on life expectancy and overall well-being. According to the WHO, obesity is a major risk factor for heart disease, stroke, high blood pressure, diabetes, musculoskeletal disorders, some cancers, and more. However, debates persist with disease proponents arguing that obesity meets the criteria for a disease due to its adverse effects on health and associated genetic factors, while opponents view obesity as a preventable risk factor arising from lifestyle choices. Regardless, addressing obesity requires a holistic approach, combining education, policy changes, individual empowerment, and efficacious and safe pharmaceutical options.

Glucagon-like peptide 1 (GLP-1) agonists, originally designed to manage type 2 diabetes and regulate blood sugar levels, have found a new role in obesity treatment and management. These medications mimic the effects of the naturally occurring hormone GLP-1, which responds to food consumption. While several GLP-1 agonists exist, only 2 (Wegovy and Saxenda) have secured approval from the US Food and Drug Administration (FDA) for chronic weight management in individuals who are overweight or obese and do not have type 2 diabetes. Recently, the FDA approved Zepbound for chronic weight management in adults who are obese or overweight with at least 1 weight-related condition such as high blood pressure or type 2 diabetes. Additionally, GLP-1 agonists like Ozempic, initially intended for diabetes treatment, are sometimes prescribed off-label for weight loss. These drugs work by reducing appetite and promoting weight loss, but it's crucial to remember that their effectiveness hinges on consistent use alongside diet and exercise. Weight regain is likely once the medication is discontinued. However, these pharmaceutical interventions are expensive, costing around $10,000 to $15,000 per year on average in the United States.

> The impact of these medications extends across the entire healthcare system, affecting pharmaceutical companies, pharmacies, employers, health plans, and weight-loss companies.

The impact of these medications extends across the entire healthcare system, affecting pharmaceutical companies, pharmacies, employers, health plans, and weight-loss companies. By 2035, half of the world's population could meet the criteria for being overweight or obese, leading to potential costs exceeding $4 trillion annually. In the United States, legislation allowing Medicare Part D coverage for obesity treatment could

result in costs ranging from $13.6 billion to $26.8 billion if 10% of beneficiaries use these medications. However, adherence to long-term medications, as well as their safety and potential abuse, remains a challenge, emphasizing the need for comprehensive weight-loss solutions. Additionally, some health plans are scaling back coverage due to their high prices, which can be up to 20 times higher than historical pharmaceutical interventions. Despite the effectiveness of these new treatments, cost remains a concern for stakeholders and patients alike.

Reimbursement policies play a pivotal role in ensuring equitable access to obesity treatments for patients who need them. Historically, health insurance coverage for obesity treatment was lacking and patients faced financial barriers, limiting their access to medications. We need more clinical data and real-world evidence. This involves collaboration among healthcare providers, payers, patients, policy makers, and HEOR and clinical researchers as obesity management requires a synchronized effort. This will require a long-term vision beyond immediate savings as we must envision long-term gains. Healthier populations lead to reduced downstream costs. We need to take a holistic approach that would entail reimbursement strategies encompassing lifestyle interventions, medications, and surgical options. No one-size-fits-all solution exists. If we demonstrate improved outcomes and cost-effectiveness, reimbursement barriers will crumble.

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

ISPOR, HEOR, and the Study and Treatment of Obesity

Rob Abbott, CEO and Executive Director, ISPOR

Since taking office as ISPOR's CEO in March of 2023, I've been immersed in an ongoing conversation with my staff, board, society members, and others about the overarching purpose behind our work. Put simply, "why do we do what we do?" While there is some understandable gradation in the responses, it is still possible to land on a common theme. We are united in our desire to use the scientific evidence provided by health economics and outcomes research (HEOR) to help provide the best healthcare to the largest number of people at reasonable cost. As healthcare systems globally struggle in the face of affordability challenges and increasingly complex reimbursement decisions, the availability of robust evidence to support good policy choices will become more important and relevant than ever before.

I've been thinking about this a great deal lately because while there are several markers of population health in the United States and elsewhere that have improved over the past several decades (life expectancy, the prevalence of smoking, and drug and alcohol use among youth come to mind), there is one area—obesity—in which we have not seen improvement. Many years before the word "pandemic" became ingrained in the public consciousness as a result of COVID-19, the World Health Organization (WHO) used it to characterize the alarming increase in obesity worldwide.[i] Today, the National Heart, Lung, and Blood Institute reports that nearly 3 in 4 adults aged 20 or older in the United States are either overweight or obese. The story is no better outside of the United States. In the United Kingdom, it is estimated that 28% of adults in England are obese with an additional 36% being overweight.[ii] Globally, the WHO estimates that 2.1 billion people are overweight or obese, and that 2.8 million people die each year as a result of excess weight.[iii]

In light of the above, I welcome this special theme of *Value & Outcomes Spotlight*. Obesity is a conspicuous public health problem and yet, until recently, it has been overlooked from a research and policy perspective. To be sure, there are complex physical, social, and psychological dimensions to obesity that make it difficult to "unpack," as my philosopher friends would say. Still, this should not stop us from stepping onto this particular healthcare frontier. We know that unless we do so, millions will suffer. Obesity is associated with a sharp increase in the risk of developing chronic diseases such as diabetes, cardiovascular diseases, respiratory complications, and certain cancers. It is also associated with a reduction in both life expectancy by up to 10 years in those with severe obesity and quality-adjusted life expectancy.

So, how to move forward?

ISPOR stands ready to lead further efforts to both improve our scientific understanding of obesity, and equally, to translate that understanding into practical policy and regulatory advice. Our society has already taken some important steps in this regard. In November 2023 ISPOR hosted an educational symposium that cast the economic costs of obesity into sharp relief. Using data from Canada, the United States, Germany, and Sweden, the symposium was able to highlight both **direct** (ambulance, treatment, physician visits, hospitalizations, emergency care, and so on) and **indirect** costs (absence from work, carers, work disability, reduced working capacity) annually arising from the "treatment" of obesity. The numbers below show that indirect costs are often greater than direct costs.[iv]

Table 1. Direct Costs Arising From Obesity
- Canada: 6.0 billion ($CAD)
- United States: 30.3 billion ($USD)
- Germany: 4.8 billion euro
- Sweden: 2.2 billion kroner

Table 2. Indirect Costs Arising From Obesity
- Canada: 5.0 billion ($ CAD)
- United States: 42.8 billion ($ USD)
- Germany: 5.0 billion euro
- Sweden: 2.9 billion kroner

In addition to the educational symposium on obesity, ISPOR is actively participating as a working group member with our colleagues at the International Consortium for Health Outcomes Measurement. This work included a presentation of an obesity case study at ISPOR Europe 2023. ISPOR's North American HTA Roundtable will be convening a special discussion at ISPOR 2024 on the assessment of GLP-1 products for obesity, and the international conference will also feature a workshop on valuing obesity treatments (application of generalized cost-effectiveness analysis). I should add that ISPOR's Special Interest Group on Nutrition is also hard at work on economic insights into nutrition and the value of chronic disease management, including obesity.

As the articles in this special issue of *Value & Outcomes Spotlight* make clear, there is no easy answer to the challenges of obesity. Several factors contribute to it. These include food and activity; environmental conditions; genetics; health conditions and medications; and stress, emotional factors, and poor sleep. Still, the imperative to act is real. Quite apart from the human cost, there are very significant economic costs associated with obesity. HEOR evidence can help pinpoint where policy and regulatory interventions can be most efficient and effective in addressing this particular public health pandemic.

[i] Obesity is defined as a body mass index of greater than or equal to 30, which corresponds to a weight of 221 pounds for someone 6 feet tall. The World Health Organization declared obesity a major public health problem and a global epidemic in 1997.

[ii] In Europe more broadly, it is estimated that 35% of females and 39% of males will be obese by 2025.

[iii] Obesity is a leading cause of mortality (ranked #5 globally) and is, of course, linked to various comorbidities.

[iv] Research from the United Kingdom reinforces these numbers. The annual cost to the UK health service and wider society associated with obesity is estimated to be £6.1 billion and £27 billion respectively.

HEOR NEWS

1 The Future of the Global Clinical Trial Ecosystem: A Vision From the First WHO Global Clinical Trials Forum

(The Lancet)

Clinical trial approval procedures require urgent reform, according to those gathered last November at the first WHO Global Clinical Trials Forum. "Those engaged in trials must first ensure optimal scientific and ethical design, by focusing on questions that are relevant to diverse patients and communities and making sure pivotal aspects such as sample size, populations, outcomes, and intervention design are appropriate," experts say.
Read more

2 Racial and Ethnic Inequities in the Quality of Pediatric Care in the USA: A Review of Quantitative Evidence

(The Lancet Child & Adolescent Health)

While reviewing studies published between January 1, 2017 and July 31, 2022, researchers found that the literature reveals widespread patterns of inequitable treatment across pediatric specialties, including neonatology, primary care, emergency medicine, inpatient and critical care, surgery, developmental disabilities, mental healthcare, endocrinology, and palliative care—indicating that children from minority groups received poorer healthcare services relative to non-Hispanic White children.
Read more

3 US Government Sets Rule Meant to Speed Up Insurance Approvals (Reuters)

US President Joe Biden's administration has finalized a rule requiring health insurers to set time targets for the prior authorization process for patients seeking approval for medical services under insurance plans backed by Medicare and Medicaid. The rule will begin primarily in 2026.
Read more

4 Population Confidence in the Health System in 15 Countries: Results From the First Round of the People's Voice Survey (The Lancet Global Health)

Using data from the People's Voice Survey—a novel population survey conducted in 15 low-, middle-, and high-income countries—researchers found fewer than half of respondents were health secure and reported being somewhat or very confident that they could get and afford good-quality care if very sick. The lowest support was in Peru, the United Kingdom, and Greece.
Read more

5 Physicians' Perspectives on FDA Regulation of Drugs and Medical Devices: A National Survey (Health Affairs)

Researchers say the findings suggest that physicians commonly lack familiarity with drug and medical device regulatory practices and are under the impression that the data supporting the US Food and Drug Administration's drug and high-risk device approvals are more rigorous than they often are. Physicians would value more rigorous premarket evidence, as well as regulatory action for drugs and devices that do not demonstrate safety and effectiveness in the postmarket setting.
Read more

6 The WHO and Drug Regulators Want to Reformulate the Flu Vaccine. It's Easier Said Than Done (STAT News)

In fall 2023, the World Health Organization and some national drug regulators urged that manufacturers remove the component known as B/Yamagata from flu vaccines as quickly as possible, citing the fact that this lineage of flu B viruses appears to have been snuffed out during the COVID-19 pandemic. However, the International Federation of Pharmaceutical Manufacturers and Associations, an organization that represents vaccine manufacturers and other pharmaceutical entities, is calling for a longer lead time for the shift, saying it will take flu vaccine makers until the 2025-2026 Northern Hemisphere cycle to be able to make the change across the board.
Read more

7 The Remote Healthcare Revolution: An Investigation Into HCPs' Perceptions of the Evolving Digital Landscape–Part 1: Telemedicine (IQVIA)

Covadonga Fernández del Pozo Bielza (Prod OpnsAnalytics Solutions), Carolina Ricarte, (Product Offering Development), and Tom Woods, (EMEA Thought Leadership) say in interviewing 1600 physicians from 11 different countries, IQVIA found that face-to-face consultations remain the dominant channel across all countries, and it is expected that the proportion will remain relatively stable in the next 6 months to come. Additionally, while Italy and the United Kingdom have the highest remote consultation shares, Japan had the lowest.
Read more

8 E&C Investigation Uncovers Earliest Known SARS-CoV-2 Sequence Released Outside of China (House Energy & Commerce Committee)

The House Energy and Commerce claims that that a SARS-CoV-2 sequence was submitted to GenBank, the National Institutes of Health's genetic sequence database operated by the National Center for Biotechnology Information, on December 28, 2019—2 weeks before the Chinese Center for Disease Control and Prevention (China CDC) first released the virus's sequence. "The existence of a SARS-CoV-2 sequence days before the Chinese Communist Party (CCP) acknowledged an outbreak, and more than 2 weeks before the China CDC release their sequence, calls into question how early the CCP knew about the virus and how long they withheld this information from the world, resulting in more deaths and wasting critical time to develop vaccines and treatments."
Read more

9 Testosterone Treatment and Fractures in Men with Hypogonadism (NEJM)

Researchers found that among middle-aged and older men with hypogonadism, testosterone treatment did not result in a lower incidence of clinical fracture than placebo. Additionally, the fracture incidence was numerically higher among men who received testosterone than among those who received placebo.
Read more

10 Chinese Hospital Finds New Genetic Sequence for Rare Blood Type P During Routine Tests (South China Morning Post)

Modern Express Post reported that the previously unknown nucleotide sequence in a person with the rare blood type p, a subtype of the P blood group, was found during routine blood tests last year at a hospital in Taizhou, Jiangsu province. The genetic sequence has been submitted to the GenBank sequence database in the United States, which has said the nucleotide sequence present in the sample had not been detected previously anywhere in the world.
Read more

ISPOR 2024–2025

TOP10 HEOR TRENDS

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Leveraging the Power of RWE

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3 Artificial Intelligence

Using AI and Advanced Analytics in Healthcare

4 Fostering Innovation

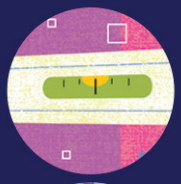
Financing Innovative Health Technologies

5 Health Equity

Addressing Healthcare Disparities

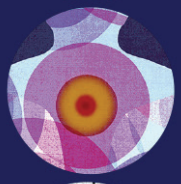
6 Accelerated Drug Approvals

Developing Evidence for Regulatory Use



7 Value Measurement

Assessing Value and QALY Alternatives



8 Patient Centricity

Engaging Patients in Healthcare Research

9 Precision Medicine

Applying HEOR to Personalized Medicine

10 Public Health

Bringing Economic Evaluation to Public Health Policies

RESEARCH ROUNDUP

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

A 2022 update on the epidemiology of obesity and a call to action: as its twin COVID-19 pandemic appears to be receding, the obesity and dysmetabolism pandemic continues to rage on.

Boutari C, Mantzoros, CS. *Metabolism*. 2022;133:155217.

Summary

The study by Boutari and Mantzoros discusses epidemiological updates for obesity prevalence in the light of new research and information that has improved our understanding of the pathophysiology of the disease and advances in therapeutic options. For example, the authors report that the prevalence of being overweight and obese has reached as high as 60% among adults in Europe. Further, over the course of 1980-2002, the age-standardized prevalence of obesity in global populations has increased from 4.6% to 14%. This increase was the largest in the United States (6.8% in 1980 to 22.4% in 2019), followed by Europe (8.4% in 1980 to 20% in 2019). The authors state that inaction to prevent these increases may result in 2.7 billion adults being obese by the end of 2025.

Relevance

The authors stress the rapid increase in obesity rates over the past decade. Its prevalence is higher in the female population and increases with age. Further, the prevalence also varies across regions and globally. The authors describe the rapid increase in prevalence as the "obesity pandemic" and suggest collaborative efforts between governments, the scientific community, as well as the food industry to help mitigate this crisis by promoting healthy lifestyle modifications.

The economic burden of obesity.

Vuik S, Lerouge A, Guillemette Y, Feigl A, Aldea A. In: *The Heavy Burden of Obesity: The Economics of Prevention*. OECD Health Policy Studies. OECD Publishing, Paris, 2019. Accessed February 7, 2024. https://doi.org/10.1787/67450d67-en

Summary

In this book chapter, the authors provide data on population health and economic impacts due to obesity. Based on findings from the Organization for Economic Co-operation and Development (OECD) model, the authors further describe the impact of obesity across 52 countries (OECD, EU28, and G20 countries), focusing on individual-level factors including life expectancy, morbidity, mortality, and health expenditures. Finally, the authors also describe the impact of obesity on country-level factors including the gross domestic product and tax rates. The authors report that the United States (USD PPP 645 per capita), Germany (USD PPP 411 per capita), and The Netherlands (USD PPP 352 per capita) will have the highest spending on obesity. In contrast to the United States (14% of healthcare budget), Estonia will spend < 5% of its healthcare budget on obesity and overweight conditions. The healthcare spending burden for obesity will be primarily driven by its impact on conditions like diabetes, cardiovascular diseases, dementia, and cancer.

Relevance

Through this study, the authors describe the multifold impact of obesity, which is far reaching not only to population health but also on a country's economy. Mitigation strategies and public health initiatives are required to limit the impact of obesity on health expenditure, labor markets, and a country's gross domestic product.

A prescription for achieving equitable access to antiobesity medications.

Wright DR, Guo J, Hernandez I. *JAMA Health Forum*. 2023;4(4):e230493-e230493.

Summary

In this article, the authors discuss the promise of new antiobesity medications (AOMs) as well as the potential challenges that patients may have accessing these new pharmacological treatment options. It is estimated that approximately 142 million individuals (or about 40% of the US adult population) meet the clinical criteria for these treatments. However, due to their current pricing (approximately $1000 per month), the new AOMs fall about 40% to 60% higher than commonly accepted willingness-to-pay thresholds, and hence, are not cost-effective. Further, health disparities are exacerbated due to the higher prevalence of obesity in underserved populations and associated lack of access to AOMs due to their high costs. The authors propose a multistakeholder approach involving pharmaceutical manufacturers (accessible pricing), payers (favorable coverage decisions for beneficial longer-term outcomes), physicians (decision support), and researchers (observational studies to display safety, cost-effectiveness analysis) that can help improve access to AOMs, better manage a patient's obesity, and in turn prevent adverse diabetes and cardiovascular outcomes.

Relevance

Both shared and individual efforts from stakeholders can help ensure equitable access to novel AOMs that can mitigate harmful outcomes of obesity.

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

ISPOR Conferences and Events

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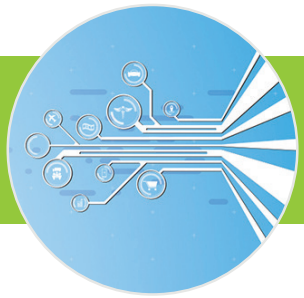
ISPOR Patient-Centered Research Summit 2024 | May 5



The ISPOR Patient-Centered Research Summit 2024 will be held in Atlanta, GA, USA on Sunday, May 5.

This is a colocated event with ISPOR 2024. The goal of the ISPOR Patient-Centered Research Summit 2024 is to advance patient-centered research by fostering collaboration between the ISPOR researcher and patient communities. The summit provides a global platform for sharing developments in patient-centered research, patient-engagement methods, and policies that support the incorporation of this evidence into regulatory, and value and health technology assessment processes. This summit will seek to optimize the impact of patient engagement in evidence generation and healthcare decision making.

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- Differentiate between outcomes research and clinical research, listing pros and cons of each.
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- Describe and demonstrate the techniques of cost-minimization, cost-benefit, cost-effectiveness analysis, and cost-utility analysis.
- Describe and define the skills/concepts of sensitivity analysis and budget impact analysis.

February 28-29 | 10:00AM – 12:00PM EST (Virtual)
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Introduction to Clinical Outcome Assessments (COAs): Selecting, Modifying, or Developing Fit-for-Purpose Measures

What you will learn in this introductory level course:

- 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.

March 13-14 | 10:00AM – 12:00PM EDT (Virtual)
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What you will learn in this introductory level course:

- Describe the concepts of variability, uncertainty, causality and effectively interpret probabilistic sensitivity analysis.
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- Use the good research practices of the ISPOR-SMDM Joint Modeling Good Research Practices Task Force to understand when and how the selected modeling technique should be incorporated into an economic evaluation.

March 27-28 | 10:00AM-12:00PM EDT (Virtual)
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February 14 | 10:00AM – 11:00AM EST

Patient WAIT Survey Findings Across 8 LATAM Countries

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- Show actionable information
- Gain insight into relevant information
- Understand general information on potential bottlenecks for access to innovative medicines post-FDA approval.

February 27 | 11:00AM – 12:00PM EST

Measuring Value in Oncology: Are We Keeping Pace With Science?

What you will learn in this webinar:

- Increase awareness and further empower people with cancer to participate in value assessments
- Add to the science of oncology-relevant endpoints and leverage PROs
- Evolve value assessments, manage uncertainties and assess overall impact.

April 3 | 6:00PM – 7:00PM EDT

Measuring the Indirect Costs Driving Financial Toxicity in Oncology

What you will learn in this webinar:

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- Recognize the need for incorporation of financial toxicity into economic evaluation
- Become aware of current methodological approaches to incorporate financial toxicity into economic evaluation.

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Measuring THE PROMISE of Obesity Drugs

BY CHRISTIANE TRUELOVE

For many people, ringing in 2024 means resolutions to lose weight and be healthier. It's a pattern that will be repeated as obesity and inactivity rates continue to rise. According to the World Health Organization, worldwide obesity has nearly tripled since 1975. In 2016, more than 1.9 billion adults 18 years and older were overweight, and of these, more than 650 million were obese.

In Trust for America's Health's September 2023 report on the antecedents and rates of obesity in the United States, the organization stated that the national adult obesity rate has increased by 37% and the national youth obesity rate increased by 42% since the group published its first obesity report in 2004. Trust for America's Health says the increases show obesity is a society-wide, population-level issue. "It's critical to recognize that obesity is a multifactored disease involving much more than individual behavior," said J. Nadine Gracia, MD, MSCE, President and CEO of Trust for America's Health. "In order to stem the decades long trend of increasing obesity rates we have to acknowledge that the obesity crisis is rooted in economic, health, and environmental inequities. Ensuring all people and communities have equitable opportunity and access to healthy food and physical activity is fundamental to addressing this crisis."

Obesity rates are increasing in Europe and Asia as well. The European Commission in August 2023 estimated that 52.7% of the adult (aged 18 and over) population in the European Union (EU) was overweight in 2019. In looking at the EU member countries as well as Norway, Turkey, and Serbia, the commission reported that the proportion of overweight adults varied in 2019 between 37% in Italy and 58% in Croatia for women, and between 53% in France and 73% in Croatia for men. In 2019, for the population aged 18 years and over, the lowest proportion of women considered to be obese was observed in Italy at 10.7%, and for men in Romania at 11.1%. The highest proportion of women considered to be obese were recorded in Malta at 26.7%, while for obese men the highest share was found in Croatia at 23.7%. Data were derived from the European health interview survey.

> "In order to stem the decades long trend of increasing obesity rates we have to acknowledge that the obesity crisis is rooted in economic, health, and environmental inequities."
>
> – J. Nadine Gracia, MD, MSCE

The Asian Development Bank Institute reported in June 2017 that more than 40.9% of adults in the region are overweight compared to 34.6% in 1990. "Overall, our estimates suggest the total costs caused by obesity to be 12% of total healthcare expenditures or 0.78% of gross domestic product in the region. Obesity is thus a serious threat to the prosperity of the region and calls for urgent action," write Matthias Helble and Kris Francisco.

Enter the GLP-1s

While the chatter about glucagon-like peptide receptor-1 (GLP-1) drugs reached a fever pitch in 2023 (in December, Science named GLP-1s its 2023 Breakthrough of the Year), drugs in the class had their debut more than 15 years ago. First came Bayer's Byetta (exenatide) in 2004 for the treatment of type 2 diabetes. Novo Nordisk launched liraglutide (Victoza) in 2009, which gained approval by the US Food and Drug Administration (FDA) for obesity in 2014. In 2017, Novo Nordisk received its first US approval for semaglutide, which is marketed as Ozempic for the treatment of type 2 diabetes. Novo Nordisk launched a weight-loss version of semaglutide, Wegovy, in 2021.

> "For those battling obesity, these medications can offer a supportive boost, but the real transformation emerges from a comprehensive lifestyle overhaul."
>
> – Phyllis Pobee, MD

Semaglutide kicked off intense demand for a few reasons. First, the drug is a once-weekly injection, compared with exenatide and liraglutide. Second, clinical results released in 2021 showed that patients lost 15% of their body weight in 16 months. Then in August 2023, a study in the *New England Journal of Medicine* revealed that patients with heart failure and obesity who took semaglutide had almost double the heart improvement. Novo Nordisk announced that same month the results of a study of 17,000 people (published in November in the *New England Journal of Medicine*), which found patients on semaglutide had a 20% lower risk of fatal or nonfatal heart attacks or strokes than those on placebo.

Novo Nordisk has been struggling with supply chain difficulties for Ozempic and Wegovy. Though the company has taken a number of measures to address this, the European Medicines Agency in December 2023 announced a shortage of Ozempic 1 mg, 0.5 mg, and 0.25 mg pre-filled pen. The agency attributed the shortage to increased demand and manufacturing capacity constraints, and predicted that it will continue throughout 2024.

Meanwhile, a new GLP-1 drug has entered the market. In November 2023, Eli Lilly received FDA approval for tirzepatide, the active drug in its type 2 diabetes medication Mounjaro, to be marketed as Zepbound for obesity. Back in July, Lilly had released results from its SURMOUNT-3 trial for tirzepatide showing additional 21.1% weight loss after 12 weeks of intensive lifestyle intervention, for a total mean weight loss of 26.6% from study entry over 84 weeks. While Lilly is still in

the process of producing cardiovascular data for tirzepatide, several physicians speaking with Reuters in December stated that they believe that the drug will show a similar heart benefit to Wegovy.

Always and Forever?

Physicians recognize the potential of new medications as part of a broader treatment strategy for obesity," explains Phyllis Pobee, MD, a family practice physician and weight-loss coach with a focus on comprehensive health solutions encompassing cosmetic and weight loss medicine. "While these drugs can play a role in reducing appetite and supporting initial weight loss efforts, it's imperative to integrate them within a holistic framework that includes dietary changes, physical activity, and psychological support. For those battling obesity, particularly with concurrent health conditions, these medications can offer a supportive boost, but the real transformation emerges from a comprehensive lifestyle overhaul. The clinical success of these medications underscores their value as one component of a multifaceted approach to sustainable health and wellness," says Pobee.

> "The focus on pharmaceutical solutions may overshadow the importance of lifestyle changes. A holistic approach to obesity, including diet, exercise, and behavioral therapy, is often more sustainable."
>
> – Phyllis Pobee, MD

In her practice, Pobee has guided patients through comprehensive weight loss journeys, where some have experienced significant weight reductions of 30, 40, or even 50 pounds, using medications as one element of a broader, personalized health and lifestyle strategy.

According to William Samuel Yancy Jr, MD, MHS, a specialist located at Duke Lifestyle and Weight Management Center, his practice is using "considerably more" medications than it did just 2 or 3 years ago, due to patient and physician interest. "I see 20 new patients a week. And that's just me, we have 5 other medical providers doing this. We're seeing 40 to 50 new patients a week and prescribing these medicines to many of them."

However, both physicians state that the reliance on medication raises concerns. The long-term side effects of this class of drugs are not fully understood, and this uncertainty poses a risk to users, Pobee says. "Moreover, the focus on pharmaceutical solutions may overshadow the importance of lifestyle changes. A holistic approach to obesity, including diet, exercise, and behavioral therapy, is often more sustainable. Such methods not only address weight loss but also encourage overall health improvements."

Yancy says patients need to understand that drugs such as Wegovy and Zepbound are not a "magic bullet." "They work through the eating plan, just like bariatric surgery. These medications are a tool that helps people to adhere to their eating plan more closely. They reduce hunger, they can make you feel full faster, they can even reduce cravings."
He adds that these drugs must be paired with a sustainable, healthy eating plan as well as exercise. That's because some patients might continue eating the same unhealthy foods yet lose weight—but instead of losing mostly fat, they might lose muscle and can suffer nutritional deficiencies. Providers also need to be able to explain the side effects of the drugs, such as nausea, to patients and address them appropriately.

Yancy points out that the way many insurance companies who cover the medications want physicians to administer the drugs could also cause unintended effects. Insurers sometimes require physicians to increase the dose every month, rather than letting the patient stay on a lower dose for a longer period of time when needed. But if patients lose weight too fast, complications could occur. Rapid weight loss can lead to gallbladder disease or gallstones, bone loss, dehydration, hair loss, and even electrolyte abnormalities that lead to cardiovascular issues such as arrhythmias. "Also, if you have to ramp the dose too quickly, the patient may be less likely to learn a healthy eating plan."

Both Pobee and Yancy expressed concerns that patients may have to be on these medications long-term because once they are off the drugs the weight comes back.

Yancy has seen this occur. "I have a patient who was taking the medicine and then the supply ran out and he couldn't get it. He's been off of it for 3 or 4 months now and he's gained back 40 pounds."

> "These medications are a tool that helps people to adhere to their eating plan more closely. They reduce hunger, they can make you feel full faster, they can even reduce cravings."
>
> – William Samuel Yancy Jr, MD, MHS

The patient had initially lost weight through a low carbohydrate eating plan and then had hit a plateau, Yancy says. He requested and was prescribed Wegovy. "We added the medicine and he made more progress and was in a really good spot, but then he couldn't get the drug at his pharmacy. He ended up regaining the weight that he lost with the medicine, in addition to some of the weight that he lost with the eating

plan. That's because the medicine can distract you from the eating plan."

Despite these concerns, Yancy and Pobee see the potential benefits of these drugs from a societal perspective in improving quality of life and possibly saving costs for hospitalizations related to diabetes and heart disease—although how payers and health plans see the value of these medications still remains to be seen.

> "Cost analysis on these medications indicates they are currently the costliest prescription drugs paid for by the plan on an annual basis."
>
> – University of Texas health system executives

Yancy says one area that is understudied, when it comes to the value of weight-loss interventions, is measuring the use of other medicines in treating comorbidities of obesity such as type 2 diabetes and hypertension. "When we have patients losing weight in the clinic, we frequently have to cut back on our medicines—and to me, that's one of the best barometers of how their disease control is going." And while Ozempic specifically reduces blood glucose, patients may be able to reduce other medicines they take for their diabetes, "I still think that's a meaningful outcome."

According to Jonathan Levin, PhD, policy researcher at the RAND Corporation, improved coverage of these drugs could save downstream costs resulting from the complications of untreated obesity or untreated type 2 diabetes. "There's potentially a financial incentive there, depending on the lag time from the increased cost of taking the medication versus reduced costs later," he says. "At this point, it's hard to say when those financial savings would be realized."

Levin says payers also need to account for the commonly known side effects of the GLP-1s—particularly nausea and constipation—in looking at why patients may not be sticking with these drugs as well as they should. "As a researcher, what we may observe is that patients—whether or not it's in their best interest or their health—may stop taking the medication for those reasons. That could attenuate the positive impacts of these drugs."

This patient recalcitrance was observed by executives at the University of Texas employee health system. In September 2023, the University of Texas health system decided that as of September 2023, it would stop covering Wegovy and Saxenda (liraglutide) for its health plan members. Executives stated that the cost rose from about $1.5 million per month to more than $5 million as of May 2023. "Cost analysis on these medications indicates they are currently the costliest prescription drugs paid for by the plan on an annual basis, even more costly than medications for complex conditions like cancer," executives said.

In monitoring compliance with these medications under the plans, the university saw that less than 46% of users remain on the medication. "This equates to a significant cost to the plan with less than desirable compliance with medication and treatment protocols," executives said.
While some patients were benefiting from using these medications for weight loss, "the plan is not seeing the expected reduction in cost for other conditions a member may be attempting to control as a result of using Wegovy or Saxenda," executives said. "These savings are not being realized due to the excessive cost the drug manufacturer charges for the weight-loss medication."

The University of Texas is not the only payer who has decided to stop covering GLP-1s for obesity. On January 25, the state of North Carolina's governing board for its health plan voted that it would stop paying for weight-loss medications as of April 1, 2023. Health plan executives say that the cost for GLP-1s prescribed for weight loss has increased from about $3 million per month 3 years ago, to more than $14 million per month in 2023, before manufacturer rebates. In total for 2023, trustees estimated the cost of Wegovy, Zepbound, and Saxenda to be $170 million before rebates, and $102.2 million with rebates applied. Costs were projected to exceed $600 million annually before rebates within the next 5 years.

> "Manufacturers will need to go beyond the standard contracting approach and think differently about how they approach federal, state, and city governments and structure rebates in a creative manner to make sure patients get access to GLP-1s."
>
> – Jonathan Levin, PhD

While the state decided in October 2023 to grandfather in obesity patients already taking GLP-1s, CVS Caremark, who administers the health plan, told executives that the state would lose all rebates for these drugs if it did not restart the weight-loss therapy program. Before losing the rebates, the plan was paying $880 per member per month. Without the rebates, the price went up to $1349 per member. In total, if the rebate had remained at the 2023 level, the plan would have paid $85 million for its grandfathered members. With the rebate, the cost would rise to $139 million.

Because of these well-publicized high costs, Levin believes that manufacturers will need to go beyond the standard contracting approach and think differently about how they approach federal, state, and city governments and structure rebates in a creative manner to make sure patients get access to GLP-1s.

Eli Lilly's experiment

On January 4, 2024, Lilly announced the launch of LillyDirect, a website that the company calls an "end-to-end digital healthcare experience" for US patients living with obesity, migraine, and type 2 diabetes. The company says LillyDirect offers disease management resources, including access to independent healthcare providers, tailored support, and direct home delivery of select Lilly medicines—including Zepbound, which Lilly CEO David Ricks says hit 25,000 new prescriptions per week at the end of December—through third-party pharmacy dispensing services.

"We know that people have come to depend on the efficiency and convenience of digital solutions to meet a variety of their everyday needs—healthcare being one of them," stated Frank Cunningham, group vice president, global value and access at Lilly. "We launched LillyDirect with the hope that it will offer patients an innovative end-to-end experience to manage their health and access their medicines, so they can get back to living their lives."

The website offers lists of area physicians who provide telehealth services as well as in-person visits. However, Yancy doubts that these services will be able to improve patient access to Zepbound. "The reason that patients are having trouble accessing the medicine is because their insurance doesn't cover it," he says. "They either can't get it because their insurance is not covering it or the supply is not there. So, having more providers is not really going to help the issue."

Another potential problem is that in looking at the list that LillyDirect provides of physicians in his area, Yancy found some physicians he knows are practicing weight-loss medicine—such as himself and all the physicians at his practice—have been left out, and others who are included do not know they are listed.

"I spoke with the chief of endocrinology at Duke [David D'Alessio] and he said, 'Oh, I didn't know I was listed.' He then looked at the list and said, 'Oh, that person's not even seeing patients anymore. And that person works at the VA, so they can't see patients in the public. And that person retired.' So some of the providers on Lilly's website may not know that they're listed, and some of them may not even able to prescribe these medications."

The role of ISPOR and HEOR

Research done by ISPOR members will play a particularly important role in helping payers—whether private insurance or government entities—figure out if they should cover these new obesity drugs, how they should be prescribed, and how to pay for them.

Research presented at ISPOR Europe 2023 addressed the growing use of GLP-1s for obesity. A poster, "Real-World Prescribing of GLP-1 RAs Among Patients with Overweight or Obesity in the United States," presented by authors from Truveta, looked a large and diverse real-world dataset and found that new prescribing of GLP-1 receptor agonists among patients with obesity has increased since 2021, including new prescriptions for type 2 diabetes-labeled medications to patients with no evidence of type 2 diabetes. A second poster by authors from Envision Pharma Group, "Overview of Recent Systematic Literature Reviews on Glucagon-like Peptide-1 Receptor Agonists for Weight Loss in Adults with Obesity," sought to identify key trends in the literature on the use of GLP-1 RAs in adults with obesity. While recent systematic literature reviews reflect the growing use of GLP-1s for obesity, their long-term benefits are not yet known. Researchers from both poster presentations indicate that additional work is needed in this area to synthesize the existing evidence on anti-obesity medications to better understand the initiation, adherence, and outcomes among patients newly prescribed GLP-1 RAs.

Christiane Truelove is a healthcare and medical freelance writer.

SUGGESTIONS FOR FURTHER READING:

- Social Media Research to Understand Reported Efficacy of GLP-1 RAs for Weight Loss
- Clinical Outcomes of Semaglutide 2.4 Mg in Patients with Obesity or Overweight in a Real-World Setting: A 6-Month Retrospective Study in the United States
- Costs and Outcomes of Increasing Access to Bariatric Surgery- Cohort Study and Cost-Effectiveness Analysis Using Electronic Health Records
- Cost-Effectiveness and Value of Information Analysis of Brief Interventions to Promote Physical Activity in Primary Care

By the Numbers: Growing Rates of Obesity

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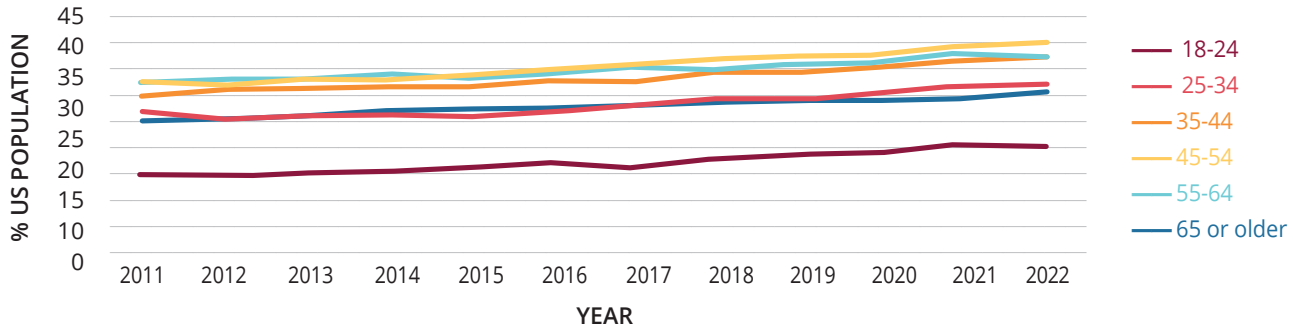
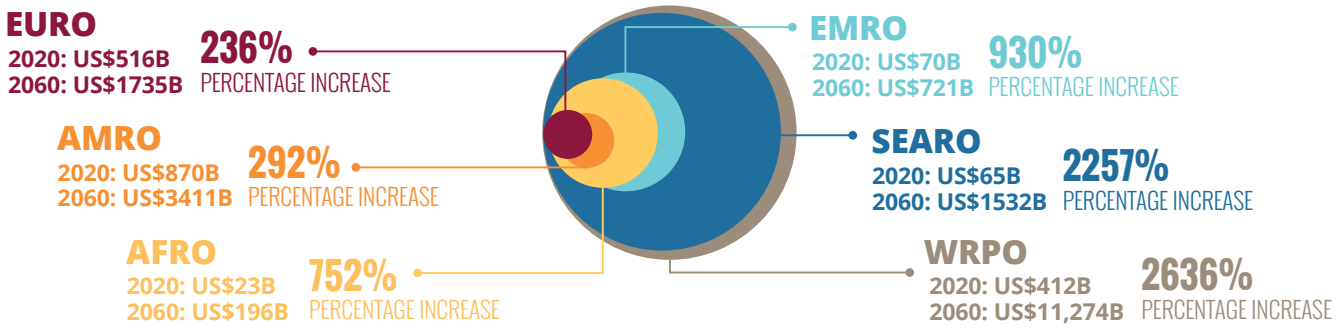
Percentage of Obese Adults in the United States by Age Group



Economic Impact of Obesity Around the World: Current and Future



AFRO = Africa, AMRO = North & South America, EMRO = Middle East & North Africa, EURO = Europe, SEARO = South & Southeast Asia, WPRO = East Asia & Pacific

Expected Trends in Comorbidity Incidence and Spending Associated With Obesity

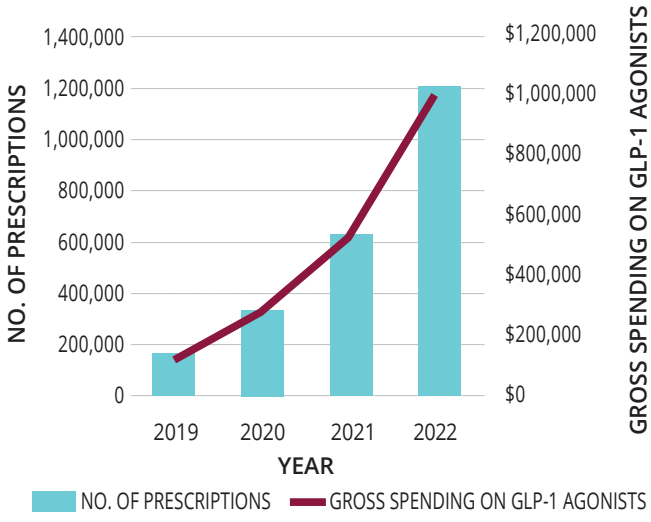
Over the next 30 years (2020-2050), obesity is expected to cause:

- **212 million** new diabetes cases
- **462 million** new cardiovascular disease cases
- **17 million** new cancers
- **31 million** new dementia cases

Over the next 30 years (2020-2050), obesity is expected to account for:

- **70%** of all diabetes-related health expenditures
- **23%** of all cardiovascular disease-related health expenditures
- **9%** of all cancer-related health expenditures
- **18%** of all dementia-related health expenditures

Medicaid Utilization and Spending on New Weight-Loss Drugs, 2019-2022



Solving the Real-World Evidence Challenge for US Payers: A Call to Action for Pharma

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Given the focus on healthcare spending and ongoing marketplace evolution - including the IRA - payers are increasingly seeking innovative solutions for delivering healthcare in a cost-efficient manner.

This has necessitated a greater focus on evidence appraisal to understand drug value, and Real-world evidence (RWE) presents payers with a powerful tool which can transform healthcare decision-making and improve population health management.

Through a series of payer interviews, this paper delves into the reasons why the use of RWE by US payers remains limited, and recommends opportunities to improve RWE usage to enable data-driven decisions in healthcare and improve patient outcomes.

The views in this text represent the opinions of the authors, and do not represent the views or opinions of their respective organizations.

Introduction

The healthcare landscape continues to grapple with marketplace economic pressures to control spending, magnified by the continued financial impacts of the COVID-19 pandemic. In addition, with the impending implementation of the Inflation Reduction Act, payers are under increasing strain to deliver healthcare in a more cost-effective manner. In this changing landscape, real-world evidence (RWE) presents payers with a powerful tool, which, when combined with randomized clinical trial data, can help better interpret the value of therapies for reimbursement decision making. However, RWE utilization in payer value assessments remains low, despite its potential (**Figure 1**).

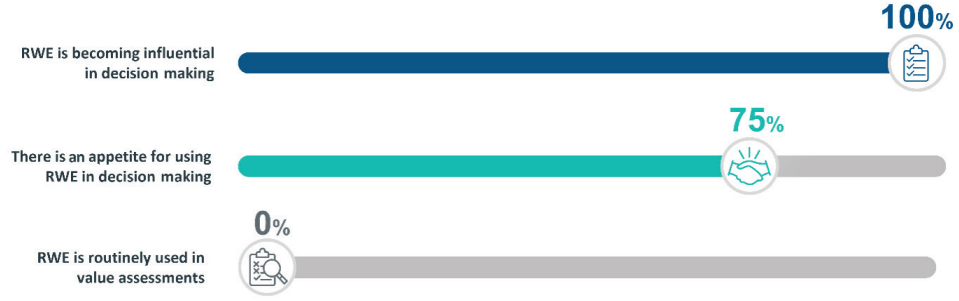
This pharmaceutical industry perspective, authored by RWE experts from industry and IQVIA, part of the "RWE Leadership Forum," aims to identify and address barriers hindering the widespread adoption of RWE in healthcare decision making. Through a collection of informal interviews with key US healthcare financing stakeholders (pharmacy benefit managers [PBMs], private health plan executives, health technology assessment [HTA] leaders, and leading academics) and a literature review supplemented by author experience, this paper examines the current and future state of RWE, exploring challenges, opportunities, and recommendations to enhance its uptake.

The evolving role of RWE

Increasing marketplace pressures to reduce cost and further demonstrate value are driving the need for additional evidence generation. In August 2022, the expansive Inflation Reduction Act was signed into law, including healthcare-specific provisions aimed at reducing drug costs for the federal government and patients.[1] These include granting the Centers for Medicare & Medicaid Services (CMS) powers to negotiate drug pricing, a Medicare Part D redesign, maximum patient out-of-pocket caps, and prescription drug inflation rebates. These provisions and subsequent increased pricing pressures will be key drivers altering current evidence requirements and evaluation standards.

With healthcare spending in focus globally, payers are seeking innovative solutions for evidence appraisal, cost modeling, and contracting. Drug price negotiation in particular is expected to be a catalyst for enhanced rigor in evidence generation. With a significantly higher proportion of the cost of drugs falling on commercial payers, more comprehensive bodies of evidence and

Figure 1: Common sentiments on the evolving use of RWE among US payers.



Source: Interviews conducted with key US payers (ie, pharmacy benefit managers, private health plan executives, HTA leaders and leading academics).

RWE indicates real-world evidence; US, United States.

value demonstration will be required to inform decisions and justify risks.

High-quality RWE presents an opportunity to transform healthcare decision making and unlock improved population health management. Recent technological advancements are now enabling faster, more patient-centric and cost-effective generation of observational evidence, as newer and more effective modalities of data linkage combined with improved real-world data (RWD) collection through wearables and electronic medical record systems are increasing data availability. This is leading several organizations to create large in-house real-world datasets covering their target populations and enabling evidence-based healthcare decision making.

RWE has gained significant traction within regulatory submissions in the past decade, with the US Food and Drug Administration (FDA) releasing guidelines on its use in submissions and 90% of new drug approvals in the United States including RWE in 2020.[2] However, the incorporation of RWE in decision making by US payers has been slow and limited to select cases, which is further illustrated by the summary of our US payer interviews as outlined below.

Challenges and barriers

Five key challenges currently hindering the routine use of RWE were identified through expert interviews with US payers (**Figure 2**). Understanding and addressing these challenges will be the first step in paving the way for RWE to be better utilized in future payer value assessments, thus unlocking its full potential for substantive applications in healthcare decision making.

1. There is a poor understanding of optimal use of RWE for payer decisions. The true value of high-quality RWE can only be realized when applied to the appropriate situations to support decision making. Due to limited opportunities to collect relevant data before market authorization, the use of RWE in initial submissions beyond natural history and standard-of-care data is limited. The highest value for RWE is likely during reassessments of drugs, in situations such as formulary evaluations and treatment sequencing decisions, as there are far greater opportunities to collect relevant RWD at this stage.[3] Some stakeholders, such as the Institute for Clinical and Economic Review (ICER), have recognized the value of RWE in reassessments and moving towards a life-cycle approach with regular reassessments.[4] However, the majority of respondents stated that they do not regularly use RWE in drug value assessments and pointed to poor communication by pharma companies on the specific value of RWE for payers.

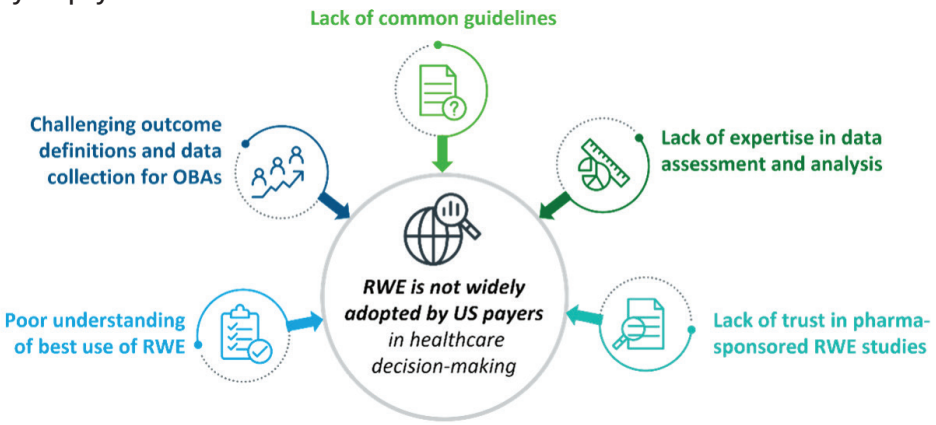
2. Outcomes-based agreements' real-world outcome metrics are challenging to define and measure. Innovative contracting, particularly through outcomes-based agreements, has emerged in recent years as a potential solution to address the increased financial pressure and uncertainty over long-term efficacy presented by novel precision medicines. RWE serves as the basis for these agreements, providing information on the real-world performance of therapies. All interviewed payers expressed high interest in defining outcomes-based agreements centered around RWE. However, the adoption of such agreements has been slow due to difficulties in defining and measuring relevant real-world outcome metrics. The lengthy timelines for determining the success and value of therapies in these agreements also pose challenges to decision makers who face shorter-term budget review cycles. As a result, simpler rebate models are often preferred over high-risk outcomes-based agreements.

3. There is a lack of common guidelines for evaluating RWE during value assessments. While some frameworks for real-world study execution exist,[5,6] there are currently no consensus guidelines for US payers on the interpretation and evaluation of RWE. Varying guidelines originally designed to address regulatory requirements or custom-made value assessment frameworks are typically used among payers, and many are using tools designed for evaluating randomized clinical trials, to assess RWE, despite significant methodological and structural differences between the study types. Additionally, there are currently no tools available for interpreting RWE in combination with evidence from randomized clinical trials.[7]

4. Payers lack expertise in data assessment and analysis for RWE studies. Even within the regulatory setting, there are widespread and varied concerns over the methodological approaches used in real-world studies, including data collection issues, study design flaws, and poor analytical approaches.[3,7] Furthermore, several respondents noted a lack of consideration for payer requirements, such as poor representativeness or relevance to payers' populations of interest.

5. There is a historic lack of trust in pharma-sponsored RWE. Poor transparency in the processes by which pharmaceutical companies generate and publish real-world studies has

Figure 2: Five key challenges hindering widespread adoption of RWE use by US payers.



Source: RWE Leadership Forum in collaboration with IQVIA.

OBAs indicate outcome-based agreements; RWE, real-world evidence; US, United States.

contributed to this lack of trust and was consistently cited as a key reason for not including RWE in value assessments. The absence of regulatory requirements to publish intentions and protocols prior to conducting RWE studies, as is required for randomized clinical trials, raises concerns over selective publishing and potential conflicts of interest.[3,7,8] Indeed, some payers highlighted they would only accept RWE in a value assessment if the research had no affiliation with pharma and was published in a reputable peer-reviewed journal.

Recommendations to pharmaceutical companies

The pharmaceutical industry will need to actively address these barriers to improve value assessment of new medicines. We recommend 5 specific actions to improve RWE utilization and realize its potential in decision making (**Figure 3**):

1. Engage early: Collaborate with payers in study design and execution to foster a productive relationship. By involving payers in data collection and/or analysis, pharma can reduce payer hesitation and educate on the best practices for data generation and usage.

2. Enhance trust and confidence in RWE: Improve transparency and scientific merit of RWE. Where possible, make study details publicly available, including intent, data sources, analytical strategy, and expected output. Engage payers throughout the study, address their requirements, and be open to critique on methodological approaches.

3. Invest in payer education and universal frameworks: Educate payers on evaluating and interpreting RWE. Provide tools, education, and expertise to enhance payer capabilities. Support the development of consensus guidelines and frameworks for evaluating RWE in standalone studies or combined with randomized clinical trial data.

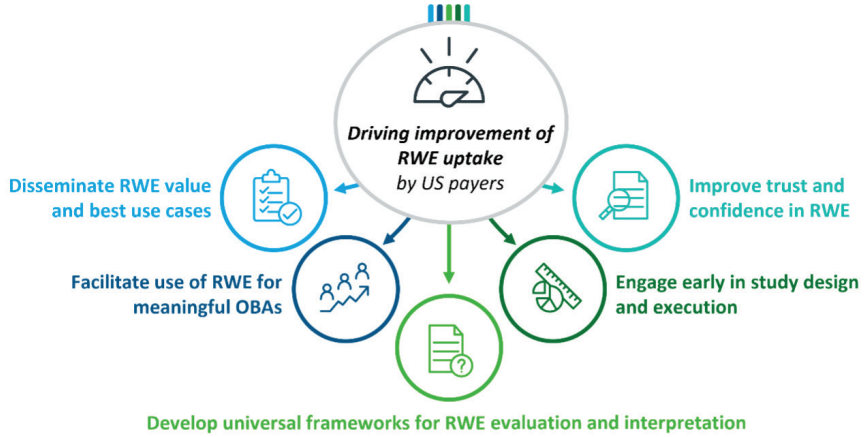
4. Discuss the value of RWE for payers: Translate RWE findings into payer-relevant messaging, emphasizing cost-effectiveness and impact on specific patient cohorts. Educate payers on the value of RWE throughout a product's life cycle, including real-world performance, safety monitoring, and drug interactions.

5. Facilitate meaningful outcome-based agreements: Address the lack of appropriate outcome metrics, measurement systems, and data availability for outcomes-based agreements. Engage with payers during study design to ensure outcomes and measurements are relevant and meaningful for patients and payers. Foster collaboration among key stakeholders, including healthcare providers and patient advocacy groups, to define data collection structures and invest in universal optimized data infrastructure (eg, Observational Medical Outcomes Partnership).

Conclusion

As interest in RWE continues to grow and data collection and analysis capabilities become more powerful, RWE offers immense potential for payers to better understand the true performance of therapies. Economic pressures and the need for long-term drug evaluations will increase the importance of considering RWE in value assessments. However, barriers such as payer mistrust, inadequate guidelines and education, and difficulty incorporating RWE into supply contracts have hindered it from reaching its potential in the US healthcare system. By building this trust, investing in education of its applicability, and opening dialogues with payers to guide mutually beneficial studies, efforts from pharma will facilitate better adoption of RWE in drug value assessments and ultimately improve patient outcomes by allowing decision makers to make data-driven treatment decisions and select the best therapy for every patient based on the full body of evidence.

Figure 3: Five recommendations for pharmaceutical companies to directly address the 5 challenges hindering RWE uptake in critical appraisals.



Source: RWE Leadership Forum in collaboration with IQVIA.

OBAs indicate outcome-based agreements; RWE, real-world evidence; US, United States.

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How Can Manufacturers of Orphan Drugs for Rare Diseases Optimize Clinical Trial Design for Market Access Across the United States, France, Germany, and the United Kingdom?

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When evaluating orphan drugs for rare diseases, US payers prefer clinical trial durations of 12 months, while payers in France, Germany, and the United Kingdom accept 6-month trials.

Payers interviewed across the United States, France, Germany, and the United Kingdom expressed low concern with smaller sample sizes in clinical trials for orphan drugs for rare diseases.

For placebo-controlled clinical trials for orphan drugs for rare diseases, payers in France and the United Kingdom may conduct indirect comparisons, with a comparator of their choice.

Open-label extension data for orphan drugs for rare diseases are not valued in France or Germany but are important in the United States and the United Kingdom.

Implications

Payer preferences for clinical trial design for orphan drugs for rare diseases differ across the United States, France, Germany, and the United Kingdom. Gaining a better understanding of these preferences can help manufacturers to best design clinical trials in order to achieve favorable market access in each country.

Introduction

Rare diseases impact around 60 million people in the United States and Europe. More than 6000 rare diseases have been identified; most have no cure, and often, no drugs with demonstrated efficacy.[1]

Orphan drugs for rare diseases offer significant clinical benefits in high unmet-need populations; therefore, payers have historically provided more flexibility in reviewing these drugs for market access decisions compared to conventional drugs.

Furthermore, health technology assessment (HTA) bodies are willing to make exceptions to traditional cost-effectiveness analyses when reimbursing orphan drugs for rare diseases; therefore, these drugs often launch at a higher price point compared to conventional drugs. Notably, orphan drug prices are closer between the United States and Europe, compared to conventional drug prices. For example, a 2021 study found that conventional prescription drug prices are, on average, 2.56 times higher in the United States compared with other nations.[2] However, a 2022 comparison of orphan drug prices in the United States versus Europe found that the average price ratio is 1.64.[3]

An analysis of the top 10 self-administered pharmacy benefit drugs by US Wholesale Acquisition Cost as of year-end 2021: Zokinvy (ionafarnib), Chenodal (chenodial), Myalept (metreleptin), Actimmune (interferon gamma-1b), Cinryze (C1 esterase inhibitor), Takhzyro (lanadelumab-flyo), Ravicti (glycerol phenylbutyrate), Oxervate (cenegermin-bkbj), Mavenclad (cladribine), and Juxtapid (lomitapide) found that 9 have moderate access in the United States, while Takhzyro has the most open access in the United States. In France, 5 have an ASMR IV while 3 have ASMR V.

Figure 1: Market Access Decisions for Orphan Drugs for Rare Disease Therapies in the United States, France, Germany, and the United Kingdom

Drug	US	UK	FR	DE
Zokinvy lonafarnib	Moderate access for 72% of lives Most open access for 28% of lives	Awaiting development	ASMR IV[4]	Non-quantifiable added benefit
Chenodal chenodeoxycholic acid	Moderate access for 100% of lives	NHS England and NICE have not issued any guidelines	Not reimbursed	Non-quantifiable added benefit
Myalept/Myalepta metreleptin	Moderate access for 100% of lives	Recommended, simple discount	ASMR IV[2]	Non-quantifiable added benefit
Actimmune interferon gamma-1b	Moderate access for 72% of lives Most open access for 28% of lives	Not recommended	Not reimbursed	Non-quantifiable added benefit
Cinryze C1 esterase inhibitor (human)	Most restrictive access for 28% of lives Moderate access for 72% of lives	Recommended, long-term use[3]	ASMR V[4]	Non-quantifiable added benefit
Takhzyro lanadelumab-flyo	Moderate access for 34% of lives Most open access for 66% of lives	Recommended with commercial agreement	ASMR IV[5]	No added benefit
Ravicti glycerol phenylbutyrate	Moderate access for 62% of lives Most restrictive access for 38% of lives	Recommended by NHS Scotland only	ASMR V[6]	Non-quantifiable added benefit
Oxervate cenegermin-bkbj	Moderate access for 100% of lives	Withdrawn/not recommended	ASMR IV[7]	Non-quantifiable added benefit
Mavenclad cladribine	Moderate access for 100% of lives	Recommended	ASMR V[8]	No added benefit
Juxtapid/Lojuxta lomitapide	Moderate access for 66% of lives Most restrictive access for 34% of lives	Authorized for use[9]	ASMR IV[10]	No added benefit

[1]Indirect comparison showed superiority for overall survival; [2]Myalepta was granted ASMR IV in generalized lipodystrophy only; [3]Cinryze is licensed for long-term prophylaxis in patients aged ≥6 years with HAE types 1 and 2 in the UK; [4]Cinryze did not demonstrate superiority vs Berinert, which received ASMR III; [5]Takhzyro was granted ASMR IV only for severe patients aged >12 years and resistant to oral treatment; [6]Ravicti was compared with Ammonaps, which received ASMR I; [7]Data are available for only Oxervate vs placebo with a weak magnitude of effect; [8]Mavenclad did not demonstrate superiority or added benefit vs other MS treatments; [9]Juxtapid/Lojuxta is authorized for use as an adjunct to a low-fat diet and other lipid-lowering medicinal products with or without low-density lipoprotein apheresis in adult patients with homozygous familial hypercholesterolemia; [10]Lojuxta was granted ASMR IV only for homozygote.
ASMR, French High Authority of Health Scale; HAE, hemangioedema; MS, multiple sclerosis.
Data for covered lives at top-3 pharmacy benefit managers, based on payer-reported data in 2022.
Most restrictive access: available only through medical exception. Moderate access: nonpreferred specialty tier, tier 3, preferred specialty tier with step edit, or prior authorization beyond label. Most open access: preferred specialty tier or managed through prior authorization to label.

DE, Germany; FR, France; NHS, National Health System; NICE, National Institute for Health and Care Excellence; UK, United Kingdom; US, United States.

In Germany, 7 have a nonquantifiable added benefit, while 3 have no added benefit. In the United Kingdom, 6 are recommended, while 1 has not yet been assessed, and 3 face restricted access.[4-6] (**Figure 1**).

This research explores how data requirements and clinical trial design for orphan drugs for rare diseases differ between the United States and Europe and provides considerations for manufacturers regarding how to design clinical trials for orphan drugs for rare diseases to maximize access and reimbursement across geographies.

Research Methodology

Primary research was conducted with payers in the United States, France, Germany, and the United Kingdom to understand payers' clinical trial design and data preferences for orphan drugs for rare diseases. In the United States, an online survey was developed and programmed in Qualtrics. It contained 53 questions and was sent through an email link to 29 payers, of which 24 responded. Payers could not advance without answering all questions and only completed surveys were recorded. Responses were collected from February to March of 2022. One qualitative in-depth telephone interview with one payer representing each of the countries: United States, France, Germany and the United Kingdom was completed in September of 2022. Payers were asked about their preferences for trial duration, sample size, placebo versus active comparator, and the impact of open-label extension data on their decisions for orphan drugs for rare diseases.

Results

A total of 24 US payers representing 116 million lives completed the quantitative survey, including 4 national managed care organization (MCO) representatives, 14 regional MCO representatives, 5 pharmacy benefit manager (PBM) representatives, and 1 state Medicaid payer. One US PBM Pharmacy Director, one government health insurance company advisor in Germany, 1 ex-Transparency Committee member in France, and 1 ex-member of National Institute for Health and Care Excellence (NICE) completed in-depth telephone interviews.

The importance of clinical trial design elements to payers across the 4 markets, in terms of their influence on the reimbursement decision, is summarized in **Figure 2**. Criteria that are categorized as "Not important" are not considered at all during decision making. For example, in Germany, open-label extension data are not important and are considered biased. "Minimally important" criteria are unlikely to be considered. For example, US payers place minimal importance on clinical trial comparators, as they routinely reimburse products that have been studied in placebo-controlled trials. "Somewhat important" criteria may be considered but are unlikely to influence the decision, whereas "Important criteria" are considered and will impact the decision. For example, open-label extension data could positively impact the formulary placement of a drug in the United States.

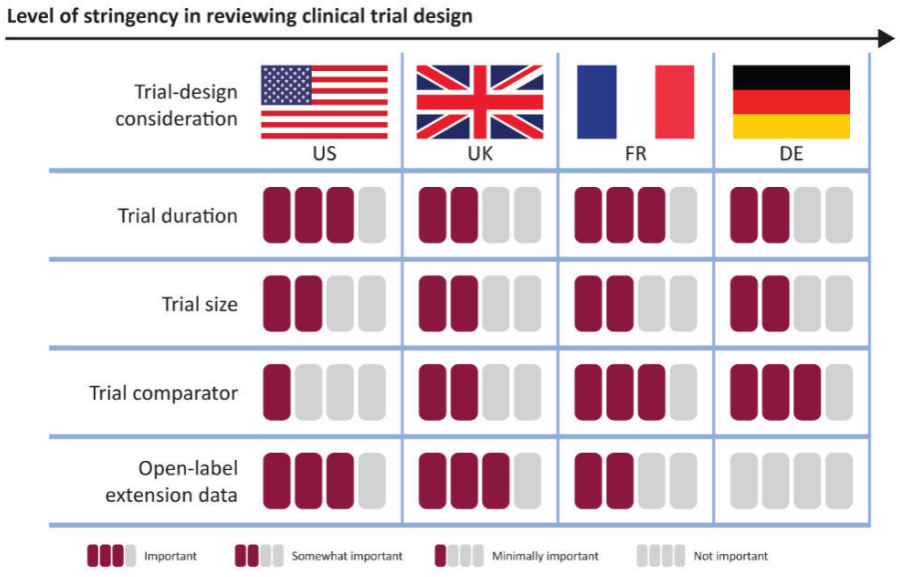
Trial Duration

In the United States, 20/24 payers indicated they are looking for trials of at least 12 months while 4 payers find trial durations between 6 and 12 months to be appropriate. In France, the payer stated that although the Transparency Committee prefers trials at least 2 years long, trials 6 months or shorter may be acceptable, especially if they involve diseases with rapid progression. They also noted that manufacturers can submit interim data for an initial coverage decision and provide additional data as they become available. In Germany, orphan drugs do not undergo a full review until they reach an annual sales threshold of €30 million. Of the 107 orphan substances reviewed by the Federal Joint Committee between January 2011 and June 2022, 20 exceeded the threshold (which was €50 million at the time).[7] It is expected that more drugs will exceed the new, lower threshold. For drugs that exceed the threshold, trial duration is a formal criterion considered during the review, and payers prefer a duration of at least 6 months. In the United Kingdom, trial duration is a formal criterion in the NICE review, and payers require trials to be at least 6 months.

Trial Size

The sample size of the trial is not a formal criterion for US pharmacy and therapeutics (P&T) committee review. Of the 24 payers, 21 indicated they are moderately concerned with smaller sample sizes for orphan drugs and for rare disease therapies, 2 indicated they are not at all concerned, and 1 indicated they are significantly concerned. The French respondent had little concern with smaller trials, noting they are more concerned about the magnitude of the benefit observed. They cited the example

Figure 2: The Importance of Clinical Trial Design Elements to Payers Across the United States, France, Germany, and the United Kingdom



DE indicates Germany; FR, France; NHS, National Health System; UK, United Kingdom; US, United States.

of spinal muscular atrophy, where the trial included 12 patients per treatment arm, and all 12 responded, resulting in a decision that the drug offered an important improvement relative to the current standard of care. In Germany, trial size is not a formal criterion, but the *P* value is. Smaller trials often lead to lower *P* values. This is problematic for drugs that exceed the €30 million sales threshold and go through a full benefit assessment. In the United Kingdom, trial size is not a formal criterion, and the respondent noted they can use other data, including natural history, to satisfy budget impact models.

Trial Comparator

In the United States, the comparator is not discussed during the P&T committee reviews, and 21 payers find placebo comparators to be adequate in measuring drug benefit. In France, Germany, and the United Kingdom, the comparator is critical to the review process, and placebo comparators are not always adequate. In France, when there is no comparator, indirect comparisons are made with the input of clinicians. In Germany, placebo comparators are considered appropriate only if no treatment alternative exists or in cases where the treatment is the last line of therapy. In the United Kingdom, indirect comparisons are used in budget-impact models. In the absence of a trial comparator, "do nothing" or "best supportive care" can be considered an appropriate comparator.

Open-Label Extension Data

Open-label extension data are valued by US payers and if they impact the prescribing information or product label, the drug is reevaluated by the P&T committee. In France and Germany, open-label extension data do not affect the reimbursement decision and the German respondent views these data as biased. In the United Kingdom, open-label extension data can improve the reimbursement decision.

Limitations

This research was limited to payers willing and available to participate in market research. In the United States, there are concerns of survey fatigue. In France, Germany, and the United Kingdom, time and budget constraints limited the research to n=1 payer per market. These are representative since these markets have centralized decision making; however, future research should pressure test findings with a broader sample in these markets and in other European markets (eg, Spain and Italy).

Conclusions

To maximize reimbursement of orphan drugs for rare diseases across the United States and Europe, trials should be at least 6 months long, but ideally 12 months to satisfy US payer preferences. Manufacturers can balance this with the fact that payers understand the urgent need to bring treatments to markets and are willing to accept shorter durations than they would for conventional drugs.

Manufacturers should focus on the quality, rather than quantity, of data when it comes to designing trials for orphan drugs for rare diseases. Small sample sizes are common for clinical trials for these drugs; however, payer concerns can be addressed with quality of study design and a demonstration of the large magnitude of patient benefit.

In the absence of a standard of care, placebo trials may be accepted across markets, although in France and the United Kingdom, payers make indirect comparisons. This should not prevent manufacturers from designing placebo-controlled trials, especially in cases where there are no existing treatment alternatives.

Although open-label extension data will not impact the reimbursement decision in France or Germany, they are valued in the United Kingdom and United States and can positively impact market access decisions, even if data become available postlaunch.

Future research should explore how legislative changes in the United States and Europe (eg, the Inflation Reduction Act in the United States and the bill on the Financial Stabilization of the Statutory Health Insurance System in Germany) will impact drug pricing and reimbursement for orphan drugs for rare diseases.

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Patient Involvement in Regulatory and Health Technology Assessment Processes: A Call for Enhanced Alignment

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Structured engagement with patients and other stakeholders is vital to increase satisfaction, transparency, trust, acceptance, and equity across stakeholders.

Many authorities encourage patients to share their experiences with their disease and treatments that subsequently improves discovery, development, and evaluation of new medicines.

Despite the move towards patient participation and systematic integration of their voice, different interpretation of patient involvement and defining it within legislation remains challenging asking for enhanced alignment and collaboration among stakeholders.

Patient Involvement and Decision Making

Patient-focused drug development (PFDD) and understanding patient knowledge and experience are increasingly becoming instrumental in drug development and associated decision making. Inclusion of patients' expertise about their lived experience brings a different and complementary perspective, compared to stakeholders who are not affected by the disease. Integrating these unique insights in decision making helps drive the development of innovative medicines, improve health outcomes, and transform healthcare. For an effective delivery of a drug within a healthcare system, patients need to trust in processes that can be achieved with greater patient involvement. Bringing new medicines to patients is dependent on 2 sequential processes: (i) the evaluation for marketing authorization by regulatory bodies, and (ii) the value assessment (eg, health technology assessments [HTAs]) for payers and reimbursement. Due to the variety of scientific requirements on how patient input should be captured, authorities and pharmaceutical companies face uncertainty in drug development decisions.

> For an effective delivery of a drug within a healthcare system, patients need to trust in processes that can be achieved with greater patient involvement.

This overview aims to compare the level of patient involvement in regulatory and HTA processes to understand convergence and divergence of approaches across major countries. This was assessed by 4 parameters: (i) overall governance framework for patient involvement, (ii) patient engagement guidance and guidelines for specific processes, (iii) institutional capacity for patient involvement, and (iv) patient community outreach and communication. Health equity is also an important topic for patients and regulators/HTA bodies, yet not the focus of the research at hand as it differs in its nature from the active involvement of patients in decision making.

Patient Involvement With Regulators in Decision Making

Since the early 1990s, the US Food and Drug Administration (FDA),[1] European Medicines Agency (EMA)[2] and Therapeutic Goods Administration (TGA, Australia)[3] have developed methodologies for patient involvement. In 2010, Health Canada,[4] Agenzia Italian a del farmaco (AIFA)[5] and Swissmedic (Switzerland)[6] joined the efforts and since then other regulators followed. In the countries in scope of this overview, frameworks are developed by most regulators to promote patient involvement systematically and consistently in decision making. (**Figure 1**)

FDA is developing a series of PFDD guidance documents[7] to address how stakeholders can gather patient experience data for drug development and regulatory decision making. It has also released guidance for Patient Preference Information in 2016.[8] EMA strongly reinforced patient involvement across regulatory activities through its engagement framework and future evolution of patient experience data in medicines' development and regulatory decision making as discussed in a workshop in 2022.[9] Patients are seen as experts like healthcare professionals and both stakeholders are encouraged to work together (eg, Patients' and Consumers' Working Party). TGA and Health Canada have structured guidelines to detail the levels of stakeholder or public engagement respectively. FDA, EMA, Health Canada, Swissmedic, and recently AIFA and TGA have a dedicated staff/office to strengthen capabilities for patient involvement reflecting the

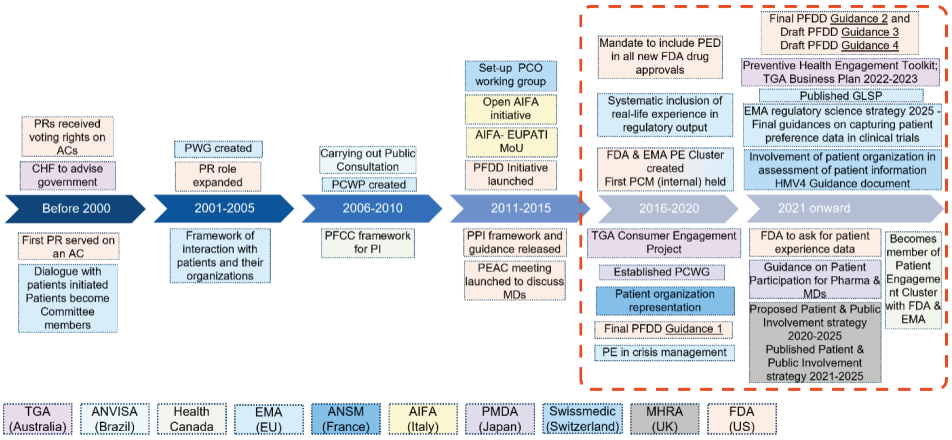
principle of equity that allows them to participate in stakeholder dialogue in a meaningful way.

In 2021, Medicines & Healthcare Products Regulatory Agency (MHRA, United Kingdom)[10] published a Patient and Public Involvement Strategy 2020-2025 defining the process of how to engage and involve the public/patients and launched a pilot program for patient involvement in drug development. Patient involvement would contribute to drug evaluations under the new Innovative Licensing and Access Pathway and safety signals, creating a benchmark against other regulators' progress. Japan's Pharmaceuticals and Medical Devices Agency (PMDA) published guidelines on patient involvement in medicines development and regulations that provide structure to patient input.[11,12] In Latin America, ANVISA (Brazil) has been carrying out public consultations on health technologies since 2008.[13] Recently, China's Centre for Drug Evaluation finalized new guidelines requesting sponsors of randomized controlled trials to consider patient needs and experience for their study.[14]

Patient Involvement in HTA Decision Making

Similar to regulatory bodies, HTA bodies are increasingly incorporating patient involvement into their processes. The Pharmaceutical Benefits Advisory Committee (PBAC, Australia),[15] Canadian Agency for Drugs and Technologies in Health (CADTH),[16] and National Institute for Health and Care Excellence (NICE, United Kingdom)[17,18] are at the forefront with patient involvement through patient community representation in HTA committees almost since 2 decades; Haute Autorité de santé (HAS, France)[19] and Red Española de Agencias de Evaluación de Tecnologías Sanitarias (RedETS, Spain)[20] began with patient and consumer groups involvement in the past few years (**Figure 2**). PBAC, CADTH, NICE, Gemeinsamer Bundesausschuss (G-BA, Germany)[18,21] and Institute for Clinical and Economic Review (ICER, United States)[22] have a well-framed guidance for patients. In addition, these organizations provide capability building resources by creating online libraries (videos, reading materials), or conducting lectures/symposia. They report back on their patient involvement

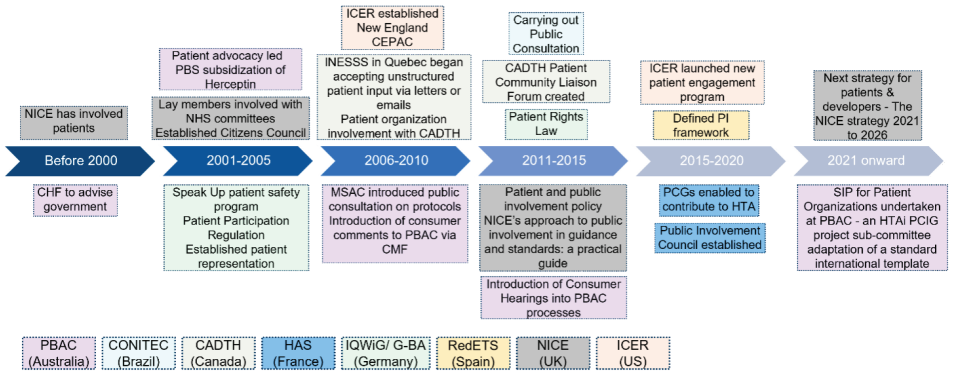
Figure 1: Timelines for Patient Involvement in Decision Making by Regulators



AC indicates Advisory Committee; AIFA, Agenzia Italian a del farmaco; ANSM, Agence nationale de sécurité du médicament; ANVISA, Agência Nacional de Vigilância Sanitária; CHF, Consumer Health Forum; EMA, European Medicines Agency; FDA, Food and Drug Administration; EU, Europe; GLSP, good lay summary practice; MHRA, Medicines and Healthcare Products Regulatory Agency; MoU, memorandum of understanding; PCM, patient council meeting; PCO, patient and consumer organization; PCWG, Patient Centricity Working Group; PCWP, Patient and Consumer Working Party; PE, patient engagement; PEAC, Patient Engagement Advisory Committee; PED, patient experience data; PFCC, patient- and family-centered care; PFDD, patient-focused drug development; PI, patient Involvement; PMDA, Pharmaceuticals and Medical Devices Agency; PPI, patient preference information; PRs, patient representatives; PWG, Patient Working Group; TGA, Therapeutic Goods Administration; UK, United Kingdom; US, United States.

Source: AIFA; BMJ; Clinigma; FDA Patient Engagement; Gov.UK; Health Canada; Partners & networks - Patients and consumers; PMDA; RSP; Swissmedic; TGA.

Figure 2: Timelines for Patient Involvement in Decision Making by HTA bodies



CADTH indicates Canadian Agency for Drugs and Technologies in Health; CEPAC, Comparative Effectiveness Public Advisory Council; CHF, Consumer Health Forum; CMF, comprehensive management framework; CONITEC, Comissão Nacional de Incorporação de Tecnologias no Sistema Único de Saúde; G-BA. The Federal Joint Committee (Gemeinsamer Bundesausschuss); HAS, Haute Autorité de santé; HTAi PCIG, Health Technology Assessment International Patient and Citizen Involvement Interest Group; ICER, Institute for Clinical and Economic Review; INESSS, Institut national d'excellence en santé et en services sociaux; IQWiG, Independent Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen); MSAC, Medical Services Advisory Committee; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PACE, patient and clinical engagement; PAPIG, Patient and Public Involvement Group; PBAC, Pharmaceutical Benefits Advisory Committee; PBS, pharmaceutical benefits scheme; PCG, patient and consumer groups; PIN, Public Involvement Network; RedETS, Red Española de Agencias de Evaluación de Tecnologías Sanitarias; SIP, summary of information; UK, United Kingdom; US, United States.

Source: CADTH; Cambridge Core Home; HAS; ICER; IQWiG/G-BA; NICE; PBAC; RSP

efforts by sharing the meeting outcomes, annual reports, and examples on how the patient/consumer input is used. PBAC Office of HTA consultation hub and HTA Consumer Evidence and Engagement Unit help consumers and patients to be part of HTA processes. Consumer comments are summarized in the meeting minutes and noted in the public summary document for the submission. NICE publishes Public Involvement Programme annual reports with all the patient involvement statistics as well as exit interviews with patients providing feedback.

For European countries, approaches to HTA differ from country to country. Some countries rely on a national process like Germany, while other countries (eg, Italy and Spain) carry out additional processes at a local regional level leading to a fragmentation of methods within a country. This fragmentation might be overcome with the upcoming implementation of the new EU HTA Regulation in 2025,[9] including guidance on the involvement of patients and representations as experts and stakeholder from the beginning. Conitec (Brazil) has been conducting public consultations annually since 2011 and since 2021 has started working directly with patients through testimonials in its committee meetings for all assessed technologies.[13] In the United States, there is no nationwide value assessment, and it is fragmented among many stakeholders. One of those is ICER, who initiated patient engagement activities in 2010. In 2020, it launched a new program to augment its efforts to empower and partner with patient organizations to contribute substantively before, during, and even after ICER's assessments.[22]

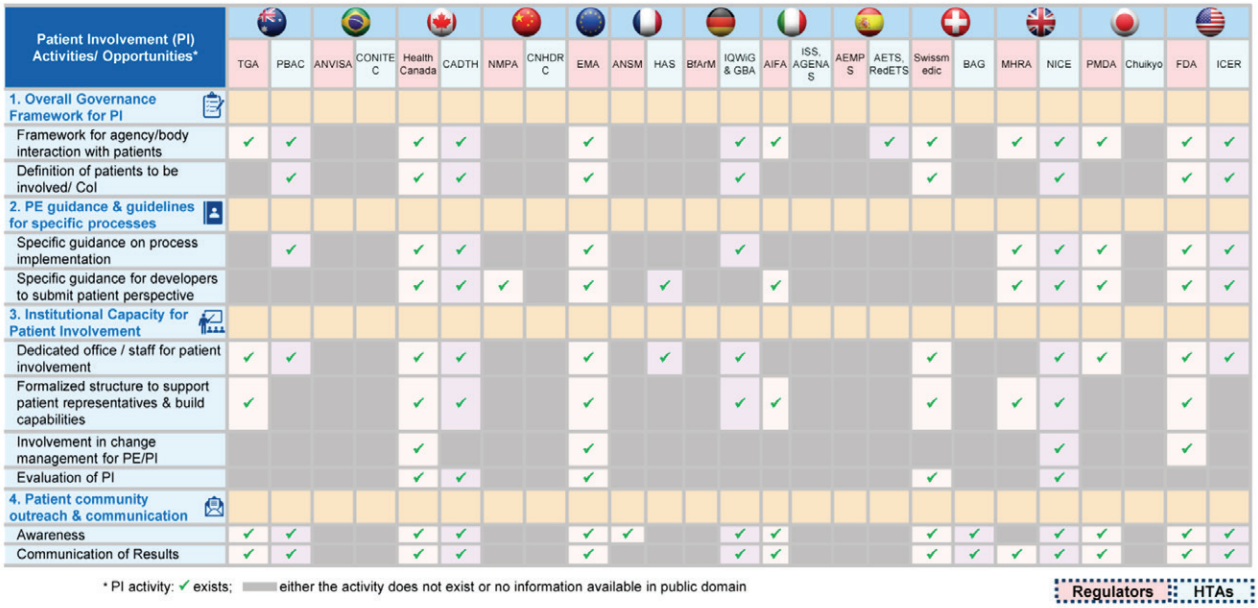
As HTA bodies focus more and more on a systematic approach to patient involvement, the act of involving patients in value assessments has long moved away from being a "tick the box" or "nice to have" activity. Patients bring different and complementary perspectives to decision bodies, and their input is critical to value assessment processes. The unique insights coming from patients help the assessors to contextualize the information provided by the sponsor of the study and submissions and to understand whether and how the new technology would or would not help address the issues experienced by patients.[23,24]

Convergence and Divergence Across Regulators and HTA Bodies Within Countries

Most authorities have included some level of patient involvement in decision making along the medicines' lifecycle. However, limited published details in English were available for Brazil, China, Italy, Japan, Spain, and Switzerland. Across the United States, United Kingdom, Canada, and Australia both the regulatory and HTA bodies have their own independent frameworks for patient involvement while in other countries only one of the 2 stakeholders published guidance (**Figure 3**).

Despite publication of many guidances, no aligned methodology across borders exists that directs how patient evidence can be collected, considered, or used during decision making. There is a clear

Figure 3: Overview of Patient Involvement by Regulators and HTA Bodies Within Countries



AEMPS indicates Spanish Agency for Medicines and Health Products; AETS, Agencia de Evaluación de Tecnologias Sanitarias; AGENAS, Agenzia Nazionale per i Servizi Sanitari Regionali; AIFA, Agenzia Italiana del Farmaco; ANSM, Agence nationale de sécurité du médicament et des produits de santé; ANVISA, Agência Nacional de Vigilância Sanitária; BfArM, Das Bundesinstitut für Arzneimittel und Medizinprodukte; CADTH, Canadian Agency for Drugs and Technologies in Health; CNHDRC, China National Health Development Research Center; CoI, conflict of interest; CONITEC, Comissão Nacional de Incorporação de Tecnologias no Sistema Único de Saúde; EMA, European Medicines Agency; FDA, Food and Drug Administration; GBA, Gemeinsamer Bundesausschuss (Federal Joint Committee); HAS, Haute Autorité de santé (French National Authority for Health); ICER, Institute for Clinical and Economic Review; IQWiG, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care); ISS, Istituto Superiore di Sanità; MHRA, Medicines and Healthcare Products Regulatory Agency; NICE, National Institute for Health and Care Excellence; NMPA, National Medical Products Administration; PBAC, Pharmaceutical Benefits Advisory Committee; PE, patient engagement; PI, patient involvement; PMDA, Pharmaceuticals and Medical Devices Agency; RedETS, Spanish Network for Health Technology Assessment of the National Health System; SNHTA, Swiss Network for Health Technology Assessment; TGA, Therapeutic Goods Administration.

Table 1: Mode of Patients' Involvement Across Organizations

Region	Regulatory bodies	HTA bodies
Australia	**TGA (Australia)** • Stakeholder input is taken via discussions, meetings, surveys, feedback, workshops, participation in advisory panels, public meetings, consultative committees, collaborating via joint projects, partnerships, or becoming member of committees • Participate via verbal/written submissions by individuals and comments from experts and associations/by patient groups and network consortiums as per their level of engagement • Stakeholders are members of statutory advisory committees, working groups, and industry consultation groups	**PBAC (Australia)** • Consumer comments/hearings; stakeholder meeting, participation in advisory committees • Consumers are members of PBAC and its subcommittees [Economics Sub-Committee & Drug Utilization Sub-Committee] • PBAC members and its committee members need to provide COIs • Office of Health Technology Assessment consultation hub and HTA Consumer Evidence and Engagement Unit (HTA CCC secretariat) help consumers and patients to be part of HTA processes
Brazil	**ANVISA (Brazil)** • Participation via public consultations (optional), public hearings (optional), and in advisory committees • Representatives of civil society are members of sectoral chambers of ANVISA	**Conitec (Brazil)** • Participation via public consultations (mandatory), public hearings (optional), in advisory committees, and health technology evaluation requests • Representatives of civil society are members of full court of Conitec and patients are members of Permanent Committee for Health Care Regulation (Cosaúde) for Agência Nacional de Saúde (ANS)
Canada	**Health Canada** • Participation via consultations, stakeholder registry, external advisory bodies, public opinion research • Consultation via advisory committee, board/council, computer-assisted participation, interactive www/e-conferencing, online discussion groups/list servers, televoting, issue conferences, nominal group process, workshops across the 3 levels of PI until the level of involvement and discussion • Citizens' engagement happens via citizens' juries, consensus conference, deliberative polling, search conference, study circles, study groups, sustainable community development, think tanks	**CADTH (Canada)** • Patients can be part of governance and advisory roles (eg, Board of Directors; Canadian Drug Expert Committee; pan-Canadian Oncology Drug Review, Expert Review Committee; Health Technology Expert Review Panel; Patient Community Liaison Forum)
Europe	**EMA (Europe)** • Representatives of European Union patients' and consumers' organizations, representatives of their own organization, as well as individual experts • Participation as experts and committee members is ruled by the EMA policy on COI • The EMA Network Strategy and the Regulatory Science Strategy recommend the advancement of standards for designing, conducting, analyzing, and reporting relevant studies incorporating robust and meaningful patient experience data for regulatory submission, and to elucidate how such data can best inform regulatory decisions	• Patient experience data are also relevant in the context of the implementation of the new HTA regulation, thus in value assessments by HTA bodies that inform subsequent decisions by payers
France	**ANSM (France)** • Participation as patient organizations' representatives or as individuals; in public hearings, and citizens' consultations	**HAS (France)** • Members of Transparency Committee responsible for evaluation of medicinal products
Germany	**BfArM (Germany)**	**G-BA & IQWiG (Germany)** • Patient participation within the German healthcare system is described at 3 different levels: (i) the macro level as active patient influence on the regulation of medical care, (ii) the meso level in terms of institutions enhancing patient information and counselling, and (iii) the micro level focusing on the actual treatment decision-making process in the medical encounter • Patient representatives at G-BA should not have any conflict of interest. People who get involved with IQWiG are also required to disclose information on potential COIs
Italy	**AIFA (Italy)** • Public consultation (patients are invited to send their comments to AIFA) • One patient organization representative is member of Pharmacovigilance Risk Assessment Committee	**ISS & AGENAS (Italy)**

Table 1 continued on following page >

Table 1: Mode of Patients' Involvement Across Organizations (continued)

Region	Regulatory bodies	HTA bodies
Japan	**PMDA (Japan)** • Patient groups provide written input • Participate in "exchange of opinions and study sessions with patient groups", meetings held by PMDA • PMDA also emphasizes that when exchanging opinions and holding study sessions, it is necessary to consider a certain level of fairness and transparency and appropriately control COI, as it is required to have a broad range of participation based on the size of the patient group and the disease area	**Chuikyo (Japan)**
Spain	**AEMPS (Spain)** • Participation via public consultations and public hearing procedures	**AETS & RedETS (Spain)** • Patients are currently involved in the development of clinical practice guidelines and shared decision-making tools
Switzerland	**Swissmedic (Switzerland)** • Patient and Consumer Organization Working Group exchange information and experiences among the participants regarding issues related to therapeutic products	**BAG (Switzerland)** • Patient organizations comment on HTA protocol
UK	**MHRA (UK)** • Patient and Public Reference Group in Innovative Licensing and Access Pathway	**NICE (UK)** • Scoping consultation (a written consultation) or scoping workshop (oral consultation)
US	**FDA (US)** • Participation via PFDD public meetings, FDA Patient Listening Session program, PEC, Patient Engagement Advisory Committee, Patient Representative Program	**ICER (US)** • ICER provides early notifications to patient groups; contacts selected patient groups directly to set up scoping calls; and accepts written feedback, information, insights, and patient testimonials. Patients can also provide oral input during the public meetings

AEMPS indicates Spanish Agency for Medicines and Health Products; AETS, Agencia de Evaluación de Tecnologias Sanitarias; AIFA, Agenzia italiana del farmaco; AGENAS, Agenzia Nazionale per i Servizi Sanitari Regionali; ANSM, Agence nationale de sécurité du medicament; ANVISA, Agência Nacional de Vigilância Sanitária; BfArM, Das Bundesinstitut für Arzneimittel und Medizinprodukte; CADTH, Canadian Agency for Drugs and Technologies in Health; CNHDRC, China National Health Development Research Center; COI, conflict of interest; CONITEC, Comissão Nacional de Incorporação de Tecnologias no Sistema Único de Saúde; EMA, European Medicines Agency; FDA, Food and Drug Administration; G-BA, Federal Joint Committee (Gemeinsamer Bundesausschuss); HAS, Haute Autorité de santé; HCPs, healthcare professionals; HTA, health technology assessment; HTAi PCIG, Health Technology Assessment International Patient and Citizen Involvement Interest Group; ICER, Institute for Clinical and Economic Review; ILAP, Innovative Licensing and Access Pathway; IQWiG, Independent Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen); ISS, Istituto Superiore di Sanità; MHRA, Medicines & Healthcare Products Regulatory Agency; NICE, National Institute for Health and Care Excellence; PBAC, Pharmaceutical Benefits Advisory Committee; PCWP, Patient and Consumer Working Party; PE, patient engagement; PFDD, patient-focused drug development; PI, patient involvement; PIP, Public Involvement Programme; PMDA, Pharmaceuticals and Medical Devices Agency; RedETS, Red Española de Agencias de Evaluación de Tecnologías Sanitarias; TGA, Therapeutic Goods Administration; UK, United Kingdom; US, United States.

need for alignment and harmonization on patient involvement and patient evidence approaches. Greater transparency and consistency across countries is needed for an impactful implementation of a patient-focused approach to medicines development. In the absence of a consistent approach across both regulatory and HTA bodies at the national, regional, or international level, it becomes challenging to systematically improve patient involvement practices, avoid duplication of patients' efforts, and develop broad evidence on patient experience.

Participation in regulatory evaluations and HTA provides patients with more understanding on how new treatments are being assessed, which benefits transparency. Patients' involvement in advisory or decision-making groups enables them to link their experiences and offer advice. In a few organizations (eg, Australia), patients are involved within stakeholder or consumer frameworks exhibiting the concept of equity to contribute in a meaningful way (**Table 1**). However, the variability of patient involvement for decision making can result in a potential mismatch of regulatory and HTA outcomes and introduces uncertainty into drug development decisions.

Efforts are ongoing to drive convergence across all stakeholders, fostering international collaboration (FDA and EMA established Patient Engagement Cluster workgroup in 2016) to exchange information and strengthen international collaboration on patient engagement. Health Canada became an official member of the Patient Engagement Cluster in 2022. Similar clusters could facilitate conversation on how to engage or involve patients, processes for selecting and preparing patients to participate, and discussion on goals to scale up future engagement. Several international platforms facilitate collaboration between the HTA bodies, such as the Health Technology Assessment International Patient and Citizen Involvement Group, HTA-Regulatory Interactions and Conditional Coverage, and the European network for HTA (EUnetHTA). Building synergies across regulatory and HTA bodies could improve clarity of the evidence

needed and lead to decisions based on a joint understanding of patient needs, including the patient involvement provision of joint scientific advice. Health equity is another topic in the area of involving patients, yet it differs in its purpose from involving patients in decision making. Regulators and HTA bodies are supporting incorporation of health equity. The FDA initiative, "Enhance EQUITY Initiative", supports diversity in clinical trials and "Enhance EQUITY of Voices" acknowledges the diversity within the patient community. The involvement of and guidance on diverse populations in decision making is a large topic that would warrant additional and separate research work. ICER has published a white paper recommending key methods through which HTA can support health equity. Health equity is equally important and related, yet a slightly different topic from the active engagement of patients in decision making. The assurance that the involved patients are representative of a diverse population is indeed an area where further efforts are needed.

Call to action for the Future

Patients bring real-life experience. Patient involvement empowers patients to play an active role in healthcare systems and is becoming a mandatory step for the drug developers during evaluations. Systematic patient involvement ensures the relevance, legitimacy, and transparency of assessments and recommendations.

The separate processes of regulatory and HTA-related patient input result in a degree of uncertainty on the patient evidence that needs to be provided by developers and requires double the capacity from the patient community. Focusing on a standard and internationally acceptable patient involvement processes across regulators and HTA bodies would help to avoid duplication, strengthen the patient evidence, and certainly increase transparency on which data are needed and how they are used. Ideally, efforts of regulators and payers should be aligned within countries and across geographies to further enhance the level of evidence and the impact patients have in healthcare systems decisions. To progress, further research is needed to evaluate the impact of patient involvement in decision making. Simultaneously, a broader discussion is required on how patient involvement can support health equity efforts and how diverse and representative populations get involved, aiming at better health outcomes and equity. Further research will be needed to address how this equity in the involvement can be achieved to drive strong patient-informed decision making across all stakeholders and patient populations.

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