

SEPTEMBER/OCTOBER 2022 VOL. 8, NO. 5

# VALUE & OUTCOMES SPOTLIGHT

*A magazine for the global HEOR community.*

## VALUING THE HEALTH OF CHILDREN

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**ISPOR**

*Improving healthcare decisions*

# VALUE & OUTCOMES SPOTLIGHT

SEPTEMBER/OCTOBER 2022  
VOL. 8, NO. 5

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

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## FROM THE EDITOR

### Valuing Health for Children

Ensuring appropriate treatment options and preventive measures such as vaccinations are important for children's health and their future. Because these treatments can be expensive and healthcare systems have limited budgets, we need to ensure children and adolescents are receiving the most effective treatments that are also cost-effective. Securing appropriate healthcare for every child in need requires generating evidence and data by utilizing appropriate methods to determine the value to place on a child's health.

Multiple pediatric generic patient-reported outcome instruments are available by age with the more frequent ones including DISABKIDS, PedsQL, CHQ, CHIP, KINDL, and KIDSCREEN. Despite the availability of these validated tools, very limited data on children's and adolescents' health related quality of life (HRQoL) are being generated and are available for review by health technology assessment (HTA) authorities. This creates a gap in evidence, which limits our understanding and ability to appropriately place value on children's health. In addition, HTA authorities have not provided clear guidance on how to measure and value children's HRQoL, apart from NICE which has done the most in this space. However, there is lack of consensus among HTA bodies and without clear guidance or frameworks, uncertainties and methodological challenges in conducting economic evaluations in children will remain.

In this issue of *Value & Outcomes Spotlight*, Wendy Ungar, MSc, PhD, highlights the key challenges to conducting economic evaluation in children which include:

- the inability to measure preferences for health states in infants, toddlers, and very young children reliance on proxies;
- the need to consider changes in resource use and health state preferences for different age groups as children mature;
- modeling costs and health consequences over the lifetime;
- using different approaches or instruments for generating utilities in different age groups;
- effects of discount rates when up-front costs are high, and benefits are deferred or accrue over many decades; and
- the need to incorporate the costs and consequences of spillover effects on caregivers and family members.

Although much progress has been made in valuing children's health, additional work is needed to further understand the preferences of children and adolescents and how to value their health appropriately. Methods used to value children's health certainly need to be improved. Methods can be employed that actively involve children in the process, taking into account their views and perspectives where possible. Patients, families, caregivers, and the public should be directly engaged to ensure their perspectives are included to capture a societal perspective. There is also an immediate need to develop consensus among HTA bodies, academia, and relevant stakeholders to develop guidelines and HTA evaluation processes. The ISPOR Emerging Good Practices Task Force on pediatric HRQoL values, planned for later this year, will also help to advance consistent and improved practices.

As always, I welcome input from our readers.

Please feel free to email me at [zeba.m.khan@hotmail.com](mailto:zeba.m.khan@hotmail.com).

Zeba M. Khan, RPh, PhD

Editor-in-Chief, *Value & Outcomes Spotlight*



## HEOR NEWS

**1 Characterizing Health Plan Evidence Review Practices**

(Academy of Managed Care Pharmacy)

Health plans tend to update their coverage policies over a 2-year period, researchers found, and in these updates they more comprehensively cite health technology assessments, randomized controlled trials, and systematic reviews/meta-analyses.

[Read more](#)**2 6 Years After Initial Pledge, Califf Launches Another FDA Program to Study the Opioid Crisis**

(Fierce Pharma)

In his second tenure as Commissioner of the US Food and Drug Administration, Robert Califf is once again calling for examination of the opioid crisis, with the agency trying to determine what's needed to support appropriate use of painkillers.

[Read more](#)**3 China's Strict Zero-COVID Measures Take a Large-Scale Toll on Youth Mental Health**

(South China Morning Post)

Experts predict that the impact of the strict lockdowns and other measures to combat COVID-19 will affect Chinese youth for years.

[Read more](#)**4 Costs Cast Cloud Over Nigeria's HPV Vaccine Plan**

(SciDevNet)

Nigeria intends to start vaccination against cervical cancer by May 2023, but the cost of the vaccine may derail those plans once more.

[Read more](#)**5 African Health Ministers Adopt New Regional Strategy to Transform Health Security**

(WHO)

African health ministers have adopted a new 8-year strategy to transform health security and emergency response in the region, with the goal of reducing the health and socioeconomic impacts of public health emergencies such as the COVID-19 pandemic.

[Read more](#)**6 Unraveling the Interplay of Omicron, Reinfections, and Long COVID**

(Kaiser Health News)

While hospitalizations and cases from Omicron infection are falling, experts are still trying to determine if the variant causes symptoms of long COVID as often or as severe as previous variants.

[Read more](#)**7 ICER Publishes Evidence Report on Treatments for Amyotrophic Lateral Sclerosis**

(ICER)

ICER evaluated AMX0035 and edaravone, finding the former comparable or better to standard of care and stating that it would be cost-effective priced at between \$9100 and \$30,600 per year. The group found edaravone comparable or incrementally better to standard of care and most cost-effective if priced between \$1400 and \$3200 per year.

[Read more](#)**8 African Health Ministers Endorse New Strategy to Curb Chronic Disease Crisis**

(WHO)

With the increasing burden of cardiovascular disease, mental and neurological disorders, and diabetes in the region, African health ministers are trying to expand access to treatments.

[Read more](#)**9 French Doctolib Platform Accused of 'Promoting Alternative Medicine'**

(The Connexion)

France's medical appointment booking site allegedly offered appointments with naturopaths and other nonaccredited practitioners.

[Read more](#)**10 Japanese Government Steps Up Efforts to Care for Women Who Miscarry**

(The Japan Times)

Municipalities in Japan are promoting mental health programs for women who miscarry, backed by the Ministry of Health, Labor, and Welfare's handbook compiled by a research team of experts for use by local governments and medical institutions.

[Read more](#)



# GETTING INTO FLOWS OF REAL EXPERIENCE: A Radical New Framework for Creating Health and Well-Being

**What is health?** If you believe you know, Chris Lawer, MA, MPhil (Oxford, England, United Kingdom), wants you to think again. As founder of Umio and the Real Experience Flow Creation® framework, his work asks us to put health back into—not separate from—real lived experience and to see it as dynamic, interactional, creational, and as a continuous flow.

Lawer says until now, the dominant way of considering health has been “intellectual analytical.” In this mode of thinking, health is separated from lived experience and is then typically split into 2 subdomains, mental and physical. For any problem (a disease condition, illness, and its symptoms), it is further abstracted to form a distinct object of intellectual enquiry.

“The object of concern is separated from an idea of normal health and from lived experience,” Lawer states. “Our gaze is, in effect, 3 times removed from the actual experience of individual persons.”

## Addressing the Problem

These now-abstract health problems are then subjected to the use of symbols and variables to record, analyze, measure, and quantify the matter of concern. “We fix it in our gaze and in time to determine its properties of size, scale, and severity to tell us what it is and what we should do about it,” Lawer says. “We then diagnose it, label it to create and share meaning, and to decide whether and how to deal with it. And then we use the same methods to assess the effect of any new or existing intervention on the properties of the problem.”

Next, Lawer explains, comes the application of logic, reason, and mathematics with outcomes, endpoints, and score systems. Together, these are used to produce the correlations, comparisons, and predictions needed to inform evaluations, choices, and actions in healthcare practice. “This dominant mode of abstract intellectual analytical thought fixes in time discrete parts of whole experience in an objectified model of health, functioning, and being,” he says. “While this mode of thought has produced huge medical advances in the 20th and 21st centuries, my position is that on its own, it’s no longer enough.”

According to Lawer, as the human condition has become more complex—from emergence of new beyond category group identities, the rise of the digital embodied mind, and new hidden forces of health inequity—health economics and outcomes research (HEOR) experts need to augment their analytical knowledge with deeper insight into concrete real experience.

**1.** There is a growing need to adopt a new mindset when looking at what health actually is, using the framework of real lived experience and how to create value around that.

**2.** According to Chris Lawer, health is currently perceived and framed as a separate domain to whole lived experience and is typically further split into separate mental and physical domains. Health problems, whether a disease or condition or symptom, are further separated from an idea of normal health and from living experience.

**3.** While the dominant mode of abstract intellectual analytical thought has produced huge medical advances in the 20th and 21st centuries, Lawer believes it is no longer enough because the human condition has become more complex with the advances of technology and chronic anxiety due to climate change and other crises.

**4.** Analytical knowledge must be augmented with deeper insight into concrete real experience, which is not just the outward-looking horizon of the 5 senses and what they sense, but the more inner experience sensations of feelings, states, and thoughts and their ongoing flow.

**5.** In a hyperconnected world, real experience is dynamic and never repeated. It is not a quantity of one sensation, but a qualitative multiplicity of interpenetrating, overlapping progressing sensations that is interactionally created.

**6.** The key to creating a new model of health centered on real experience is to frame novel enterprise purpose, learning, design, value creation, and valuation via an experience ecosystem. This is a loose, open cut-out of flowing reality for a context of real experience that includes human actors (organizations and individuals), practices, and technologies; nonhuman living and nonliving forms and entities; and various tendencies of thought, method, and design that together originate, form, differentiate, and impact upon the focal context of real experience in different ways via assemblages.

### Mapping Real Experience

How should real experience be mapped? Lawer describes the 5 essential dimensions of real experience as: (1) interiority, (2) flow, (3) qualitative progression, (4) interactional creation, and (5) a reality of collective flows in the world.

Lawer defines the *interiority of real experience* as not just the “outward-looking horizon” of what the 5 senses experience, but also the inner experience of sensations, feelings, and thoughts. “So, in this perspective, we fold in health (mental and physical) and any problems of disease or illness into interior real experience itself.”

For the second dimension, *flow*, Lawer maintains that real experience is always becoming or flowing. “By flow, I mean that time in experience is ceaselessly passing and also irreversible,” he says. “The future is always on its way to the present, and the present moment is always setting into the past.” This means in real experience nothing is ever stable or stays the same.

The third dimension of real experience, *qualitative progression*, is not a quantity of sensations going up and down a scale, but a qualitative multiplicity of interpenetrating, overlapping progressing sensations, which Lawer equates to the notes that make up a song. “We don’t hear just a single note, we hear notes in their interrelation or togetherness, forming a whole as the song passes,” he says.



“As the human condition has become more complex...HEOR experts need to augment their analytical knowledge with deeper insight into concrete real experience.”

Lawer explains that someone with chronic pain does not just experience a singular sensation of pain, which they are often told to score from 1 to 10. “Rather, we feel an interpenetrating set of progressing sensations,” he says. Additionally, the present experience is shaped not only by memory of past experiences, but also by where the person is, what they need or would like to do—all “entangled in relations of forces producing different interpenetrating sensations.”

For the fourth dimension, *interactional creation*, Lawer says real experience is not produced in the mind or computer, separate from our real-world encounters. “Rather, it’s created, enriched, and diminished via our interactions, encounters, and events that we have in our world.”

And as for the fifth dimension of real experience, a *reality of collective flows*, we should consider how there are similar often chronic real experiences shared by many people in the world. “They include real experiences with bodily diseases such as pain, mental health real experiences such as depression, and more social kinds of dis-ease experiences such as loneliness,” Lawer says. “In any single context, these can share certain origins, forces, conditions, and capacities as well as observable consequences.”

The problem is that all these 5 essential dimensions of real experience escape our dominant empirical intellectual analytical mode. “Dynamics, movement, and flow are evacuated by analytical knowledge,” Lawer says. “We hold experiences stable and therefore miss the unstable flowing nature of actual reality. Our tendencies of thought and method suppress access to the real, and lead to only a superficial knowing of experience. Our gaze does not see the continuous flows of multiplicities of sensations, feelings, and thoughts, forming concrete and often similar real experiences in a world.”

To create an alternative, radical empiricism of health means starting with a new model of real experience—one that is a dynamic, interior, flowing, becoming, and interactionally created via human events and encounters. And at the center of which are the core generative material of experience,” Lawer says. “These are the sensations or affects we have, as well as the capacities we desire to affect and be affected in order to enjoy the valued experiences we need or desire.”

Lawer says these aspects of real experience can be organized into 4 domains: (1) social/cultural, (2) material/spatial, (3) bodily/motor, and (4) perceptual/cognitive. Around this can be set a wider frame, which he calls a “focal real experience environment”—all of which supports a more substantive model of the origins, formation, and differentiation of health, disease, and illness within real experience, which Lawer describes as “a developmental model of health that goes way beyond the more baseline, functioning, and essential view of normal health.”

### Real Experience and Chronic Pain

For any real experience context, which Lawer demonstrates using his extensive work in chronic pain, he first defines the poles of the most positive and negative qualities, capacities, expressions, and desires for the context. The poles are then used to research and determine different states of real experience, their distribution, and the movements or transitions between them on a line of deterioration and a line of recovery between the poles for a population of place, which Lawer calls an assemblage.

“An assemblage is kind of like a machine that produces and differentiates real experiences. Greater than the sum of its parts of social determinants, human and nonhuman actors, tendencies, events, affects, capacities, and material things like devices, drugs, and digital technologies,” Lawer says. “An assemblage generates a particular enduring quality, content, and expression of real experience within a single context such as chronic pain. For any focal context, we can discover and map assemblages of real experience that exist around the poles of most positive and most negative experience, all within a real experience ecosystem environment.”

“Rarely do individual determinants have a direct causal correlation with discrete identifiable health outcomes, even within narrowly defined places, groups, or populations.”

This was the radical thinking and approach used to map assemblages for the diverse chronic-pain real experiences of 400,000 persons in Northern Ireland. Lawer and his team identified 6 previously hidden contingent relational assemblages of real experience, each with different qualities, expressions, and capacities of chronic pain along with the transitions between them. With the assemblages mapped, public health and healthcare actors have a completely new view of difference within a disease context and a new path towards value creation via assemblage-based policy design, assessment, and resource planning.

With his models of real experience, experience ecosystems, and assemblages, Lawer has developed “an entire end-to-end real experience (with health, disease, illness, dis-ease) learning, design, and creation framework and process to support any enterprise to pursue real experience impact in any context or place.”

### Social Determinants of Health and the Limitations of Current Frameworks

While Lawer agrees that social determinants of health should be part of health outcomes evaluation, he disagrees with the linear conceptual frameworks used to evaluate the impact of social determinants of health and points out the consequences that arise from their limitations. “It really comes back to my thinking on the intellectual analytical or



“By reducing disease-illness origins to discrete determinants, risk factors and outcomes, social determinants of health frameworks neglect the intrinsic complexity of people’s lives.”

abstract mode of thought that dominates the health sciences,” he explains. “We apply this in the same way to social determinants: we trace a line of causality between determinant effects and outcomes, and then the actions, the practices, or policies we launch on the back of that connection. Essentially, they all start from the same objectification of health as a separate domain and as a biomedical phenomenon within individual persons. This dominant narrative of upstream/downstream, I don’t think particularly helps.”

## 5 Essential Foundations of Real Experience Flow Creation®

Lawer advocates 5 fundamental shifts in thinking and approach that HEOR can make to embrace his model of creation (these can be downloaded from the [Umio Community](#)). These are:

- 1 SEE** See real experience (and health within it) as dynamic, interactionally created, flowing, emergent, and as a qualitative multiplicity of perceptions, affections, memories, and affective capacities
- 2 FRAME** Use a more substantive definition of health and well-being and apply it in the wider frame of lived or real experience
- 3 SENSE** Sense flows of real experience and understand how they originate, form, differ, and endure in groups, communities, places, and populations
- 4 KNOW** Know the limits of intellectual analysis of determinants, structure-agency, causality, emotions, bodies, needs, behavior, and outcomes
- 5 DESIGN** Design the conditions and emerge possibilities of health and well-being creation in real experience via assemblages and experience ecosystems

Find out more about real experience thinking, how to become a Real Experience Flow Creation Enterprise, and how to design and enact flow-creation via experience ecosystems at [Umio.io](#). Download a host of resources in the [Umio Community](#), or read about the model in depth in Lawer’s book, *Interactional Creation of Health: Experience Ecosystem Ontology, Task and Method*.

As he points out in a paper, “[Addressing the Social Determinants of Health via Assemblages of Real Experience](#)”, “rarely do individual determinants have a direct causal correlation with discrete identifiable health outcomes, even within narrowly defined places, groups, or populations.” While dirty air in high-traffic urban areas does have a direct correlation to childhood asthma, more often, “an entanglement of multiple contingent determinants” creates disease and generates health inequities.

“Any framework and analysis of health inequities must then abandon the idea of discrete determinant risk factors, where each risk originates and bears a direct line of causality to an (unequal) outcome,” Lawer writes. “Rather, the upstream-downstream analogy used in common social determinants of health narrative is better characterized as a mangrove swamp of interflowing, connected roots, puddles, bogs, streams, and dry land patches whose interactions produce ongoing conditions of multideterminant risk formation. Even in the case of environmentally induced childhood asthma, the determinant is not just the harmful particulate matter in the air (the single risk factor) but also the human actions, indecisions, motives, ignorance, exploitation, and discriminations that put and have kept them there. Any upstream determinant then is rarely just a single cause; it is an entanglement of meaning, matter, ideas, and tendencies as well as force, and is always connected with other determinants.”

Another problem is the huge number of social contexts and risk factors now included in social determinants thinking, Lawer says. “Its field has widened to such an extent that there’s almost nothing left out, nothing outside of collective life that does not mediate our health-disease status in some way. Every week, we see in the newspaper that such-and-such risk has been traced to such-and-such an outcome.”

Most of all, however, Lawer argues that social determinants thinking simply misses real experience. “Fundamentally, by reducing disease-illness origins to discrete determinants, risk factors, and outcomes, social determinants of health frameworks neglect the intrinsic complexity of people’s lives. They fail to see and understand how important differences in real experience play out across and within categories of determinants and social context. Consequently, they

are unable to produce the deep insights needed to guide actions that reduce health inequalities and disparities on a sustained basis.”

### Enter the Nautilus

In Umio’s logo and branding, Lawer uses the nautilus as an analogy for a new model of value co-creation or rather, flow-creation. “The nautilus propels itself by bringing in flows of water into its body and to maneuver its direction forward. Its entire existence is an interactional one in relation to the flows of water it harnesses to enact its movements.”





“Just as the nautilus intuitively understands how to use flows to propel itself and its interactions in its environment, Lawer wants enlightened enterprises to harness Real Experience Flow Creation® to not only learn about flows of real experience, but also to design, create, and emerge them.”

Just as the nautilus intuitively understands how to use flows to propel itself and its interactions in its environment, Lawer wants enlightened enterprises to harness Real Experience Flow Creation® to not only learn about flows of real experience, but also to design, create, and emerge them. “A Real Experience Flow Creation Enterprise becomes adept at understanding the flow nature of real experience and then harnesses this insight in its product, service, and platform design, its stakeholder relations, and in the interactional creation of health and well-being. All may be enacted via an experience ecosystem environment where multiple stakeholders work with shared purpose to create desired, valued real experiences. All embrace real experiences, assemblages, and flow-creation as their primary vehicles of value creation and valuation in the pursuit of real impact,” Lawer says.

### ISPOR's *Signal* Series

This article was developed from ISPOR's June 21 *Signal* episode, “The Real Experience Revolution®: Towards a New Empiricism of Health,” in which ISPOR welcomed Lawer and Daniel J. Pesut, PhD, RN, Emeritus Professor of Nursing at the University of Minnesota, for a conversation around the implications of Lawer's thinking and method for health economics, value creation/valuation, and outcomes for nursing and other key healthcare professions, and for creating health and preventing/addressing disease from the perspective of whole real experience via trans-disciplinary models of purpose and action.

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

Another *Signal* episode, “New Insights Into Advanced Therapy Medicinal Product Valuation and Outcomes-Based Pricing Experience,” was held on September 27, and focused on the Danish experience with advanced therapy medicinal product-valuation approach and development of an innovative outcomes-based pricing agreement between pharma and payers. The goals of this episode were to generate insight into the practicalities of stakeholder involvement and data requirements, and to gather overall learnings from the outcomes-based pricing agreement experience from a multistakeholder perspective. We will cover this episode more in-depth in a future issue of *Value & Outcomes Spotlight*.

## FROM THE JOURNALS

## Where are populations aging better? A global comparison of healthy aging across Organization for Economic Cooperation and Development countries

Rapp T, Ronchetti J, Sicsic J, *Value Health*. 2022;25(9): 1520-1527. <https://doi.org/10.1016/j.jval.2022.05.007>

### Introduction

Population aging is a well-documented process happening in many countries. However, the concept of healthy aging—defined by the World Health Organization as “the process of developing and maintaining the functional ability that enables well-being in older age”—is less well researched, partly because this is a complex problem that is hard to define and measure.<sup>1</sup> Previous work in this area focused on dissecting differences observed between life expectancy and quality-adjusted life expectancy at the population level. Rapp and colleagues use the theoretical framework by Grossman<sup>2</sup> on health capital (ie, where health is a durable stock that depreciates over time but can be maintained/restored by investment) to model healthy aging on an individual level. The authors develop an original microeconomic approach to estimate individuals’ physiological age from self-reported health data and compare it against their chronological age to describe the extent of healthy aging across countries.

The analysis uses data between 2004 and 2014 based on 2 multicountry surveys: (1) the Health and Retirement Survey (HRS) in the United States, and (2) the Survey of Health, Aging, and Retirement in Europe (SHARE) that includes 12 countries (Austria, Belgium, Denmark, France, Germany, Greece, Israel, Italy, The Netherlands, Spain, Sweden, and Switzerland). The population was restricted to people aged 60-89 years, and to participants having at least 3 observations (39,164 individuals).

The authors model the contribution of specific factors known to impact health—namely, frailty, limitations on the activities of daily living, and comorbidities (eg, high blood pressure and cancer)—on self-reported health status and interpret these in term of aging (Figure 1). The authors used dynamic correlated random effect model and marginal impact of health depreciation variables instead of raw self-reported health scores to account for bias of cultural reporting. Several sensitivity analyses and validation exercise have been done to examine if results are robust.

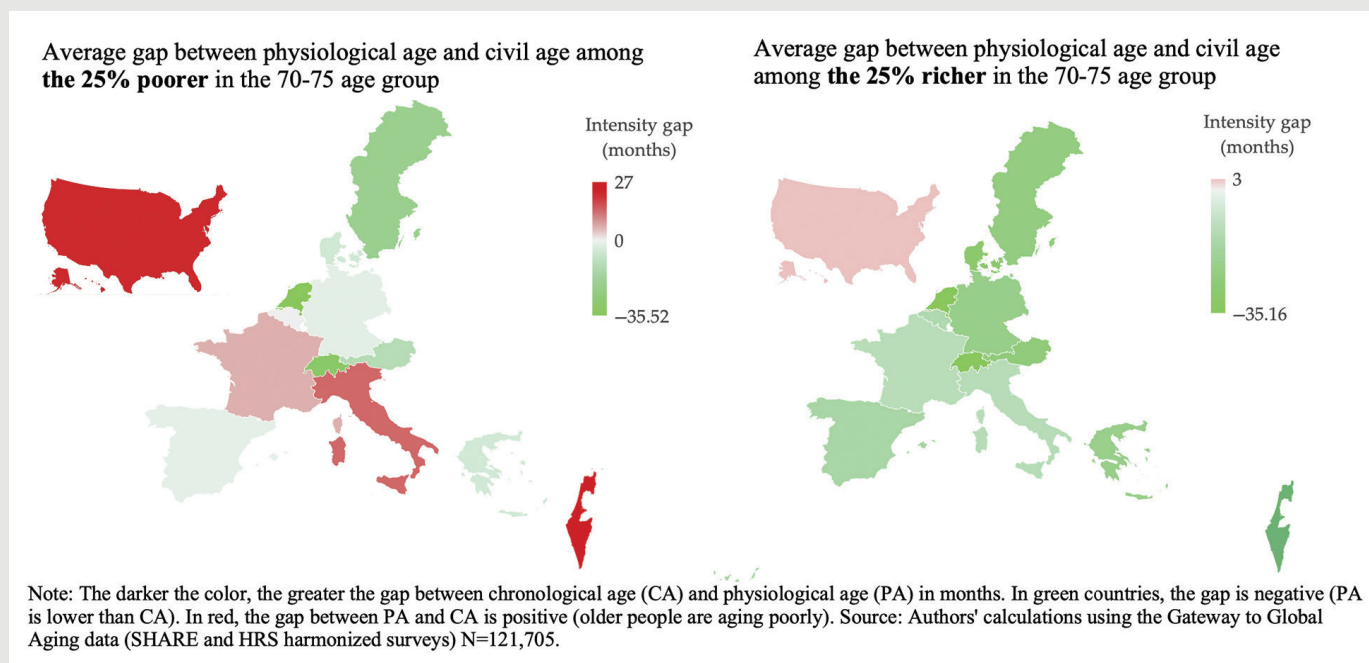
**Figure 1. Ranking of countries according to chronological age and prevalence of health depreciation indicators (descriptive statistics)**

Rank (highest to lowest)	1	2	3	4	5	6	7	8	9	10	11	12	13	Mean
Chronological age (years)	USA 74.08	Spain 72.39	Greece 72.33	France 71.55	Belgium 71.49	Sweden 71.26	Switzerland 71.17	Israel 71.14	Netherlands 71.11	Italy 70.97	Austria 70.80	Denmark 70.75	Germany 70.26	72.15
Health depreciation indicators														
Frailty (%)	Italy 17.66	Spain 16.70	France 15.91	Belgium 15.08	Austria 12.88	Israel 11.25	Germany 11.09	Netherlands 10.98	USA 9.78	Denmark 9.62	Sweden 9.22	Greece 8.41	Switzerland 7.66	12.03
ADL index (mean)	Israel 0.45	USA 0.40	Spain 0.38	Belgium 0.31	Italy 0.30	France 0.25	Germany 0.24	Austria 0.23	Denmark 0.19	Greece 0.18	Sweden 0.16	Netherlands 0.13	Switzerland 0.11	0.30
IADL index (mean)	Israel 0.65	Spain 0.46	USA 0.44	Italy 0.31	Belgium 0.31	Greece 0.29	Austria 0.28	France 0.24	Denmark 0.22	Germany 0.18	Netherlands 0.17	Sweden 0.14	Switzerland 0.10	0.33
Comorbidity index (mean)	USA 1.30	Italy 1.21	France 1.18	Israel 1.16	Spain 1.16	Belgium 1.12	Germany 1.06	Denmark 0.98	Austria 0.97	Sweden 0.94	Greece 0.94	Netherlands 0.87	Switzerland 0.84	1.14
Number of Comorbidities														
High blood pressure (%)	USA 65.41	Israel 60.17	Italy 59.75	Greece 58.12	Spain 58.03	Germany 55.78	Austria 54.46	Belgium 49.02	Denmark 47.72	Sweden 46.81	France 46.32	Netherlands 42.32	Switzerland 41.43	56.13
Diabetes (%)	Israel 30.98	Spain 24.72	USA 24.07	France 18.58	Germany 17.66	Greece 17.53	Austria 15.46	Belgium 14.91	Netherlands 14.72	Sweden 13.43	Denmark 12.97	Switzerland 10.90	Greece 9.53	19.05
Cancer (%)	USA 19.46	Sweden 13.89	Germany 13.84	Denmark 12.95	Netherlands 11.75	Switzerland 11.55	France 11.25	Belgium 10.84	Austria 9.11	Israel 8.81	Italy 8.42	Spain 7.42	Greece 3.63	13.22
Lung diseases (%)	Italy 13.48	Denmark 11.84	USA 10.96	Spain 10.91	France 10.61	Germany 10.58	Netherlands 10.54	Belgium 9.65	Austria 9.39	Israel 8.21	Switzerland 7.64	Greece 6.74	Sweden 6.17	10.24
Heart problems (%)	USA 29.97	Israel 27.12	France 21.98	Belgium 21.69	Sweden 20.88	Italy 20.28	Spain 19.94	Austria 19.87	Greece 19.85	Germany 19.67	Netherlands 19.40	Denmark 17.87	Switzerland 13.21	23.23
Stroke (%)	Israel 10.43	USA 10.22	Austria 9.96	Denmark 8.48	Belgium 8.21	Germany 8.07	Netherlands 7.36	Sweden 7.38	France 7.19	Greece 6.74	Italy 6.49	Spain 5.47	Switzerland 4.58	8.31
Arthritis (%)	USA 67.74	Italy 53.83	France 51.55	Spain 49.08	Belgium 44.87	Denmark 42.02	Germany 33.34	Switzerland 33.22	Greece 29.15	Sweden 27.04	Austria 26.13	Israel 23.18	Netherlands 18.41	47.91
High cholesterol (%)	USA 52.23	Israel 42.44	Belgium 38.64	Greece 38.33	Spain 34.06	Italy 29.78	France 29.40	Denmark 29.02	Austria 25.60	Netherlands 25.06	Germany 24.73	Sweden 20.75	Switzerland 19.08	36.71
Cataracts (%)	USA 33.00	Israel 17.36	Sweden 14.10	Spain 13.51	Denmark 13.19	Germany 13.50	Netherlands 12.97	Greece 12.56	Austria 11.65	Switzerland 11.32	France 11.20	Belgium 11.07	Italy 9.16	18.73

Note: Reading grid: country classified according to the value achieved in the dimension under consideration. Example interpretation: the prevalence of frailty is highest in Italy (17.66%), and lowest in Switzerland (7.66%). Source: Global Ageing data (SHARE and HRS surveys), 2004-2017. N=121,705.

ADL indicates activity of daily living; HRS, Health and Retirement Survey; IADL, instrumental activity of daily living; SHARE, Survey of Health, Aging and Retirement in Europe; USA, United States of America.

Figure 2. Average difference between physiological age and chronological age (in months) in the 70 to 75-year age group.



HRS indicates Health and Retirement Study; SHARE, Survey of Health, Aging, and Retirement in Europe.

The authors presented cross-country data on the difference between physiological age and chronological age for the middle of their data cohort: ages 70-75 years, considering that cross-country differences are potentially larger in this age range (Figure 2). They found that physiological age exceeds chronological age in the United States, Israel, and Italy. The authors contrast that with findings in Switzerland, The Netherlands, Greece, and Sweden that performed well (eg, Switzerland's result of -32 months physiological age to chronological age). The differences remained consistent in other age groups, even in the oldest age group analyzed.

The paper also presents inequalities in lower- and upper-income quartiles of each country, comparing them by average physiological age/chronological age differences. Widest differences were observed in the lower-income quartile (27 to -35.52 months); in the United States and Israel, the people's average physiological age is more than 2 years higher than their chronological age. Interestingly, even for people in the upper-income quartile, living in the United States is associated with positive physiological age/chronological age differences (poor aging), while in all other countries, this difference is rather negative. When exploring the socioeconomic determinants of the physiological age/chronological age

difference, the authors found that that completing higher education, having higher income, and living as a couple contribute most to healthy aging. For example, completing tertiary education on average reduces the physiological age by 1.3 years compared to the chronological age.

Apart from shedding light on intercountry differences in healthy aging, there are policy implications of the study. Retirement age, preventive measures, or healthcare interventions, such as screening and vaccination, are based solely on chronological age. Although this is administratively very simple and convenient, likely better effectiveness for social policy measures and decisions could be achieved by using the physiological age. With the methodology put forward in this research paper, the physiological age can be relatively easily calculated and used for research and for policy decision making.

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## RESEARCH ROUNDUP

Section Editor: **Aakash Bipin Gandhi, BPharm, PhD**, Research Scientist, RWE, Sanofi, Cambridge, MA, USA

### The challenges of measuring and valuing quality of life in preschool children: a retrospective review of NICE appraisals.

Lamb A, Murray A, Lovett R. *Children*. 2021;8(9):765.

#### Summary

The study by Lamb et al examined past National Institute of Health and Care Excellence (NICE) appraisals to identify methods used to measure health-related quality of life (HRQoL) among preschool children (< 5 years of age). The authors reviewed 12 NICE appraisals and found that measures usually designed for adults were predominantly used to value HRQoL among preschool children. The review revealed a strong reliance on data from adults or clinical experts for HRQoL measures in this population. Further, the instruments used to collect these data were not validated among the preschool children population. While the review committees for these appraisals acknowledge that collecting HRQoL data among preschool children is challenging, they also state that data on these aspects obtained through parents and guardians during clinical trials could be valuable inputs. Based on their review of NICE appraisals, the authors also identified several research priorities related to HRQoL measures among preschool children. These include evaluating psychometric properties of current measures, testing the feasibility and validity of valuation studies in the literature, and mapping.

#### Relevance

This study highlights the dearth in the availability of age-specific HRQoL measures as well as the lack of consensus on appropriate methods to evaluate HRQoL among preschool children. Progress in this field can help capture HRQoL aspects that matter most to preschool children and their families.

### Valuing child and adolescent health: a qualitative study on different perspectives and priorities taken by the adult general public.

Powell PA, Rowen D, Rivero-Arias O, Tsuchiya A, Brazier JE. *Health Qual Life Outcomes*. 2021;19(1):1-14.

#### Summary

The aim of the present study was to qualitatively examine the impact of different perspectives on an adult's (ie, general United Kingdom adult population) valuation of child and adolescent health states or stated preferences. Further, the study also examined how an adult's general attitude and prioritization of children's health affected their valuation of health states in

this population. Overall, the study found that participants did not display any strong preferences on prioritizing child and adolescent health over that of the general working-age adult population. The authors found that study participants' views on children and adolescent health were heterogeneous and differed by the dimension being valued. For example, study participants were more likely to give up a similar number of life years for children as they were for adults who suffer from mental health and pain conditions as compared to other conditions.

#### Relevance

The study by Powell and colleagues highlights the importance of considering the methodological impact of perspectives used when an adult sample is to be used to make valuations regarding child or adolescent health states.

### Measuring the health-related quality of life in young children: how far have we come?

Germain N, Aballéa S, Toumi M. *J Mark Access Health Policy*. 2019;7(1):1618661.

#### Summary

The article by Germain et al reviews the current status and challenges associated with HRQoL measurement among children under the age of 5. The authors found that there is a dearth of instruments for HRQoL measurements which are brief, user-friendly, and can be easily adopted in routine clinical practice, observational studies, or disease registries. Further, there is a need to develop theoretical models of HRQoL through continued research to help support valuation of health states during specific pediatric development stages of a child. Additionally, there is a need for consensus on whether parent's or proxy reporting of health states should be only limited to observable concepts versus being dependent on their input for factors including social and emotional functioning.

#### Relevance

There is a need to develop and validate age-specific HRQoL measures for valuing pediatric health to aid reimbursement decision making for payers and policy makers, especially given the rapid increase in approvals of breakthrough therapies for treating severe childhood disease conditions.

*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.*



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##### **Plenary | Wednesday, 9 November | 11:30**

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Recommendations for a Harmonized Health Technology Assessment for Digital Medical Devices Across Europe: A Multistakeholder Discussion

##### **Tuesday | 8 November | 13:30**

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Learn the basics of utilizing metamodels to negate runtime issues with computationally burdensome models and analyses. This course will cover metamodeling techniques, the design of experiments for training and validation, and performance measures for validation, as well as provide hands-on experience in R. To participate in a hands-on exercise, a laptop with RStudio installed is required.

**November 6**

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**November 17-18 | 11:00AM – 1:00PM EST**

### **Network Meta-Analysis in Relative Effectiveness Research**

Network meta-analysis (NMA) provides an integrated and unified method incorporating all direct and indirect comparative evidence about treatments. Based in part on the ISPOR Task Force Reports on Indirect Treatment Comparisons, the fundamentals and concepts of NMA will be presented, and the challenges and caveats of the networks will be evaluated. Basic knowledge of meta-analysis and statistics required.

**December 1**

**10:00AM – 2:00PM EST**

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

Learn how propensity scores can be used to mitigate the issues of bias and confounding in observational research, and the advantages and disadvantages of standard adjustment. In this course you will explore how issues of bias and confounding relate to study design, and the analysis in the setting of non-random treatment assignment where compared subjects might differ with respect to comorbidities. Some knowledge of observational databases is required.

**December 7-8 | 10:00AM – 12:00PM EST**

### **Digital Real-World Evidence Generation Approaches in Rare Diseases and Oncology**

Learn how to plan and undertake real-world evidence (RWE) studies for patient-level data through a digital app across different countries. The benefits and challenges of developing digital “bring-your-own-device” apps to collect PRO data will be discussed and analyzed as well as methods of analysis. Participants should have a basic understanding of RWE.

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

### **Introduction to Patient-Reported Outcomes Assessment: Instrument Development & Evaluation**

Learn how patient-reported outcome (PRO) measures are developed and evaluated to quantify health status from the patients’ perspective. This course includes a review of the properties of a good measure and how PRO data can be used in clinical trial or clinical care applications.

## ISPOR Education

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**October 10 | 9:30AM – 10:30AM EDT**

**Health Insurance in Africa: Sustainability in Focus**

The webinar will focus on the experience of African countries that are in the process of implementing health insurance and identifying mitigating strategies for the challenges they may face in the process.

*Brought to you by the ISPOR Africa Network*

**October 18 | 10:00AM – 11:00AM EDT**

**Achieving Fit for Purpose Data from Wearables for Age-Related Diseases**

The webinar will focus on the benefit of digital health technologies such as wearables, which can collect health-related data continuously and remotely in patients' real lives, allowing for a transformation of clinical trials and accelerated clinical development in neurodegenerative conditions.

*Brought to you by the ISPOR Clinical Outcomes Assessment Special Interest Group*

**October 19 | 9:00AM – 10:00AM EDT**

**Can the Benefits From Biosimilars Be Sustainably Increased? Policy Recommendations for Europe, Middle East and Canada**

Biosimilars offer great potential for the patients, payers, and the whole society. However, there exist policy barriers that can hinder this potential. The debate will analyze the challenges and opportunities for biosimilars uptake in Europe, Middle East, and Canada.

*Brought to you by Charles River Associates*

**November 15**

**11:00AM – 12:00PM EST**

**Different HTA Perspectives on Reliably Estimating Treatment Effects**

The webinar will focus on understanding how different health technology assessment (HTA) bodies view the use of real-world evidence to estimate comparative treatment effects for HTA submissions.

*Brought to you by the ISPOR Real-World Evidence Special Interest Group*

**December 9 | 11:00AM – 12:00PM EST**

**Strategies and Skills to Land Your First Job: The Interview**

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**Patients and Caregivers as Partners in Health Preference Research**

*Presented by Evidera, a PPD Company*

**October 20 | 1:00PM – 1:45PM EDT**

**Inclusive and Representative: How RWE Can Help to Fill Gaps Left by Clinical Trials**

*Presented by Cardinal Health*

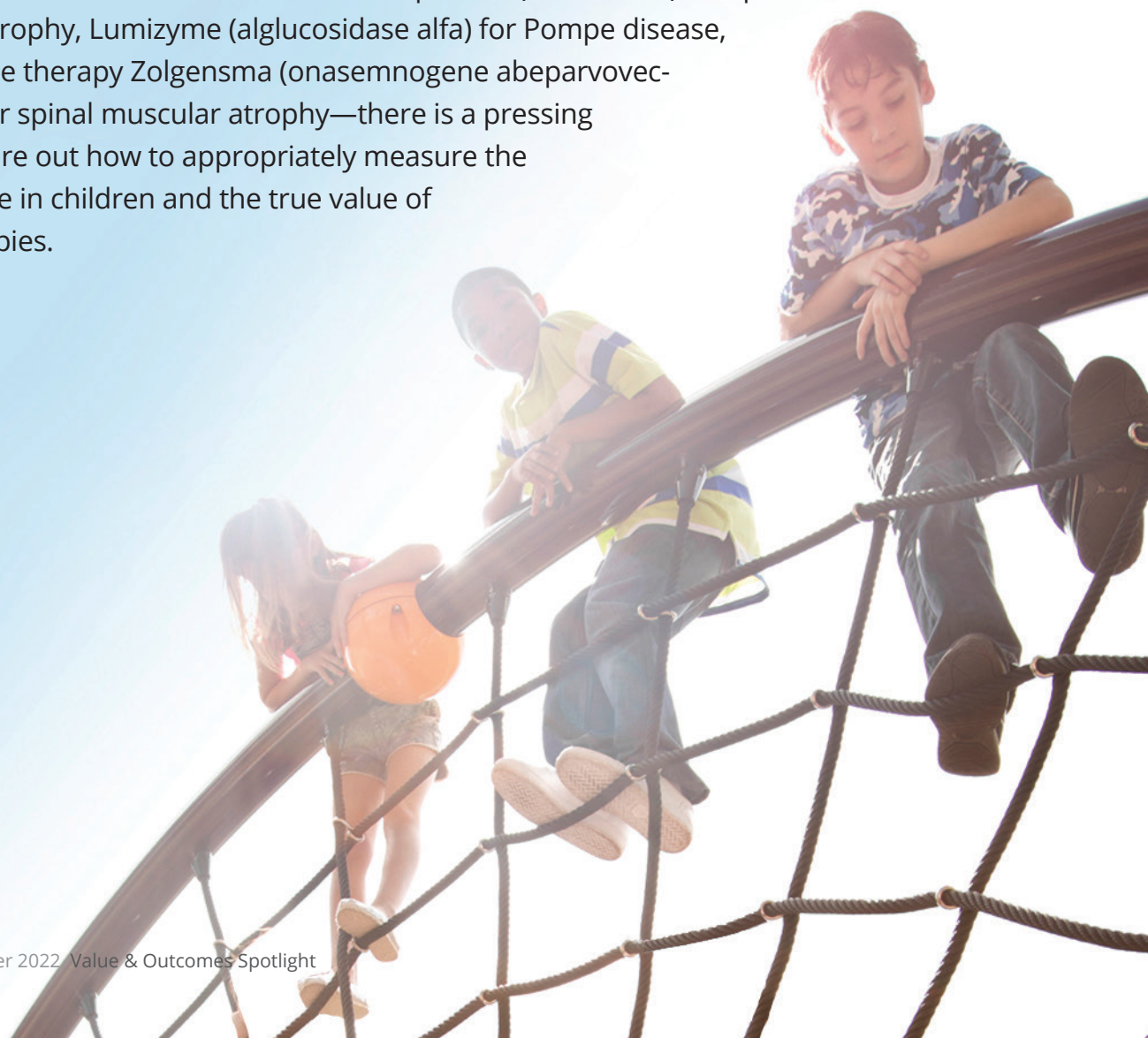
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# VALUING THE HEALTH OF CHILDREN:

## Understanding What Drives Differences in Health Preferences for Children Versus Adults

By Christiane Truelove

Ask the average person on the street about what is the value of a child's life and the automatic reply might be, "Children are priceless." But health economists and policy makers can't think this way when the health system they administer has a finite amount of money and they need to provide universal care. With the advancement of expensive therapies for treating rare diseases in children—such as Spinraza (nusinersen) for spinal muscular atrophy, Lumizyme (alglucosidase alfa) for Pompe disease, and the gene therapy Zolgensma (onasemnogene abeparvovec-xioi), also for spinal muscular atrophy—there is a pressing need to figure out how to appropriately measure the quality of life in children and the true value of these therapies.



The July 2022 issue of *Value in Health* published the results of a study led by Vivian Reckers-Droog, PhD, Erasmus School of Health Policy & Management, Erasmus University Rotterdam, The Netherlands. The paper, “[Why Do Adults Value EQ-5D-Y-3L Health States Differently for Themselves Than for Children and Adolescents: A Think-Aloud Study](#),” examined the EQ-5D-Y-3L used to measure quality of life in children and adolescents aged 8 to 15 years. The tool is the youth version of the Euroqol EQ-5D instruments developed in The Netherlands, in which patients are asked questions about different aspects of their health. The questionnaire measures 5 dimensions of patients’ health: (1) mobility, (2) self-care, (3) usual activities, (4) pain and discomfort, and (5) anxiety and depression. To obtain EQ-5D-Y-3L value sets for quality-adjusted life year calculations in economic evaluations, adults were asked about health-state preferences for a 10-year-old child. The goal of the study was to provide insight into the reasons why adults’ health-state preferences for themselves are different from those for a 10-year-old child. Additionally, researchers wanted to determine why preferences for a 10-year-old child may not be representative for the 8 to 15 years age range of the EQ-5D-Y-3L. The researchers conducted semistructured interviews using a think-aloud protocol—the participants had to explain their thoughts while answering each question—with 25 participants who performed valuation tasks for themselves, a 10-year-old child, and a 15-year-old adolescent.

### Through the Eyes of a Child? Not Quite.

According to Reckers-Droog, although the quality-of-life stages in the adult and the child versions of the EQ-5D instrument are similar, research shows these utilities differ between adult and child health states. Specifically, the first value sets that were developed in the child’s version of EQ-5D instrument showed that members of the public attribute a higher value to the health states for children than for adults with similar health states, and “there’s more noise in the data,” Reckers-Droog says. The study’s goal was to explain what drives these differences.

Researchers found that those who participated in the study were quite able to value health states for themselves, “but they really, really wanted to avoid thinking about children in bad health states with a short life expectancy,” Reckers-Droog said. “They said, ‘I just don’t want to think about this. Please get through these questions. I want to move on. This is so uncomfortable.’” This means some of the differences noted may derive from people randomly clicking on answers to get through the questions as quickly as possible.

Researchers also noted that the participants found it difficult to “give up” life years for children. If given a choice between a child living a shorter number of years but in perfect health, to a child living longer but with challenges, many opted for the longer life. “People just really didn’t want to give up any life years for improving quality of life in children,” Reckers-Droog said. “They said it’s important that the child completes primary school or secondary school. Or, ‘I feel like I’m a bad parent, but I want my child to stay with me. I know they’re in pain, but I promise I will take good care of them.’”

This means in cost-effectiveness analysis, when estimating the incremental gains that children could gain from getting access to a new treatment in comparison to the standard treatment, that if all of the values of the health states are relatively similar and high, there is not much to gain for them, Reckers-Droog points out. Technologies that may be cost-effective for adults may be less so for children because of these high and yet small differences between health states. For children, the adults will overvalue small gains in quality of life and life expectancy.

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**The public attributes a higher value to the health states for children than for adults with similar health states. Researchers found that those who participated in the study were quite able to value health states for themselves, “but they really, really wanted to avoid thinking about children in bad health states with a short life expectancy.”**

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Another thing the researchers noticed is that the adults tended to imagine different children when answering the questions. “Sometimes within the same question, they think about their own child or grandchild, the neighbor, or someone who was in their class,” Reckers-Droog said. A teacher would think about all the different children they have had in a class. And some of the participants would come up with hypothetical children, theorizing that while some would like to play outside, others would prefer to draw and don’t mind not being able to walk. This is quite different than the adult EQ-5D studies, where researchers can make sure that the study sample is relatively representative of the larger population.

There were also valuations that mattered more for adults than for children, Reckers-Droog said. When valuing the importance of self-care for an adult versus self-care for a child, respondents stated that it was more important for an adult be able to take care of themselves. “Study participants didn’t mind it so much if the children could not wash or dress themselves, because they had parents to take care of this.”

Researchers also found that not all children were equally considered when it came to mental health. Most notably, when asked about depression and anxiety in a 10-year-old versus a 15-year-old, participants expressed that “mental health was not considered to be such a bad problem [for a 15-year old], because they thought that some mental health issues are just part of puberty,” Reckers-Droog said. “An unhappy 10-year-old child was much more problematic for study participants than an unhappy 15-year-old.”

### Perfecting the Perspective

According to Reckers-Droog, the study results showed that the current valuation methods for children’s health need to be improved. “In order to compare the cost-effectiveness, or the health gains from different health technologies in different

populations, you need to be better, or you need to be more certain that you're comparing the same thing," she said.

The next iteration of this type of study may be trying to involve children in some way, but this will be difficult to do, said Koonal Shah, PhD, Science Policy and Research Programme, National Institute for Health and Care Excellence, London, England, United Kingdom. Shah is one of the authors of another paper in the July issue of *Value in Health*, "[Exploration of the Reasons Why Health State Valuation Differs for Children Compared With Adults: A Mixed Methods Approach](#)." Like Reckers-Droog's group, Shah and colleagues conducted interviews with adults and had them value health states from adult and child perspectives. These researchers found that fewer life years are traded against a higher quality of life for health states referring to children than for adults by adult respondents, resulting in higher utility values for children using standard time trade-off methodologies. "It was found that the quality-adjusted life year has a different interpretation for children compared with adults; therefore, society's willingness to pay for additional childhood life years may also be different and a youth-specific cost-effectiveness threshold may be needed to fund access to healthcare for children," these researchers said.

However, as "cognitively difficult" as it is for adults to answer these questions, there are real ethical considerations about "asking children to consider hypothetical scenarios that relate to death and dying and severe ill health," Shah says. "And you just may not get valid or reliable responses." He does say it is important to understand younger people's preferences, and "you can use alternative methods that are less cognitively challenging and don't involve explicit consideration of death."

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**The quality-adjusted life year has a different interpretation for children compared with adults; therefore, society's willingness to pay for additional childhood life years may also be different.**

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A discrete choice experiment, for example, can be applied without a death or a health state duration attribute. Shah said he was involved in research where a discrete choice experiment that had been used for adults was tweaked and used for 11- to 17-year-olds. "We did find that we got reasonable responses that suggested that adolescents were capable of expressing their preferences about health states in that way."

While the adolescents' responses were not hugely different from the adults, there were some differences, Shah said, and these justified looking at the adolescent preferences.

### Implications for Health Policy Makers

Measuring and valuing health-related quality of life for children is difficult, Shah admitted. At NICE, "we've got very well-established methods for measuring and valuing health-

related quality of life in adults, and we've struggled to make recommendations about how to measure and value health in children and younger people because there are these methodological issues."

On one hand, while it can be appropriate to base child health state values on the preferences of children because it is children who are affected by the health states, NICE and many other similar HTA bodies take a view that the preferences of the general population should be sought when generating utility values, and not necessarily those who are currently affected by a specific health state. "Many adult members of the public are taxpayers, and in a taxpayer-funded healthcare system, like we have in in the United Kingdom, it is appropriate that their views count towards how technologies are evaluated and funded," Shah said. There is also the argument that everybody, not just current patients, are potential users of healthcare in the future.

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**As "cognitively difficult" as it is for adults to answer these questions, there are real ethical considerations about asking children to consider hypothetical scenarios that relate to death and dying and severe ill health.**

---

Another argument for eliciting children's health preferences is that even though adults could be future patients, they can never be the users of a child's health intervention. Shah points out that adults, however, make decisions on behalf of children all the time, including healthcare decisions for their own kids.

"The challenge for decision makers and policy makers like NICE is to find an appropriate balance between those arguments," Shah said. "And we could do with research from ethicists and from pediatric specialists to help guide us through the various issues."

And for the future? "While we're already seeing lots of good empirical research done on the impact of different perspectives, and different preference elicitation methods, I'd like to see a focus on the normative arguments and practical considerations," Shah said. "I think that would be really helpful for informing the policies of organizations like NICE going forward."

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**Editor's Note:** In addition to the 2 articles mentioned in this story, the July 2022 issue of *Value in Health* contained a commentary by Nancy J. Devlin, PhD entitled, "[Valuing Child Health Isn't Child's Play](#)" and an article by Juan M. Ramos-Goñi et al entitled, "[Does Changing the Age of a Child to Be Considered in 3-Level Version of EQ-5D-Y Discrete Choice Experiment-Based Valuation Studies Affect Health Preferences?](#)" Follow this [link](#) to read this special collection of articles on valuing health of children in *Value in Health*.

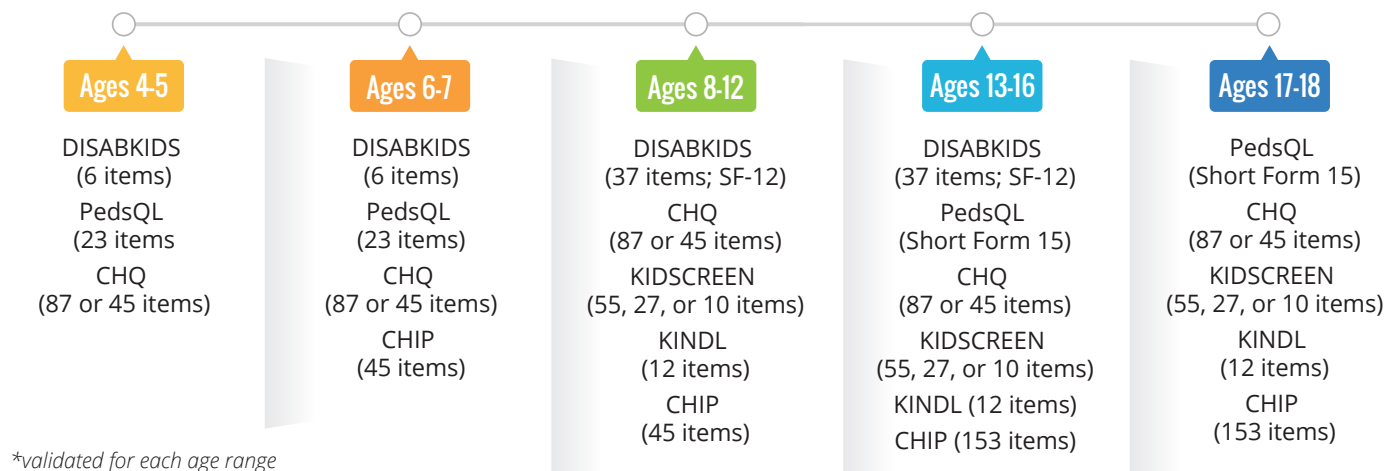


## By the Numbers: Valuing Health for Children

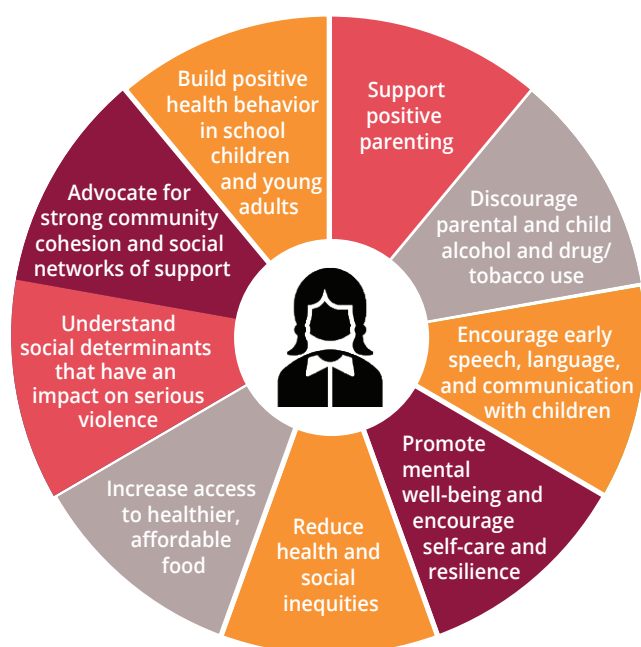
Section Editor: **The ISPOR Student Network**

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### The most frequently used pediatric generic patient-reported outcome instruments\* by age



### No child left behind: an approach to improve health outcomes for vulnerable children



*Steps to support action and reduce vulnerability and the potential harm of adverse childhood experiences*

### 5 ways to manage the power differential between children and adults in research

01•

Use methods that allow children to feel part of the research process, giving them the maximum opportunity to provide their views

02•

Be responsive to children's own agendas

03•

Involve children as part of the research team

04•

Use group interviews

05•

Check on children's willingness to participate throughout the interview, which includes being aware of nonverbal cues (ie, body language)

# The Use of Child-Specific Utility Instruments in Decision Making in Australia

Cate Bailey, PhD, MAppSci, University of Melbourne, Victoria, Australia; and Rosalie Viney, PhD, University of Technology Sydney, New South Wales, Australia; on behalf of the QUOKKA Research Project Team

Pharmaceutical Benefits Advisory Committee makes recommendations on which medicines receive public subsidy, based on assessing value for money, and generally using cost-utility analysis. Measuring and valuing quality of life is a key part of this process

When looking at medicines for children, we found that the economic models rarely incorporated child-specific approaches to measuring and valuing quality of life.

Greater use of child-specific utility measures would improve the evidence about value for money for these medicines.

## Background and Rationale

Estimating quality-adjusted life years (QALYs) is an important part of economic evaluation in healthcare. This requires robust approaches to measuring and valuing health-related quality of life (HRQoL) so that different outcomes, populations, and conditions can be compared.<sup>2,3</sup> These methods have typically been developed for adults and are often based on the use of specific instruments that have a standardized approach to measuring and describing quality of life and a preference-based scoring algorithm to provide values that can be used to estimate QALYs. Measures that are used in adults,

## Estimating quality-adjusted life years is an important part of economic evaluation in healthcare.

however, were not designed with children (persons aged under 18 years) in mind and therefore, may be unsuitable for children's development stages and inappropriate if children are asked to self-report their own health.<sup>4</sup> The methods for eliciting preferences to provide the values may also be inappropriate for children, especially when considering children's abilities at different ages. For instance, commonly used methods such as time trade-off and standard gamble ask respondents to make choices that involve trading off between length of life and quality of life and involve explicit consideration of death. Child-specific utility measures with relevant dimensions and suitable valuation methods are needed to value health improvements in health conditions in children,<sup>5</sup> leading to a funding call from the Australian government to address this need, which has established the *Quality Of Life in Kids: Key evidence to strengthen decisions in Australia (QUOKKA)* program of research (<https://www.quokkaresearchprogram.org/>).

At the start of our research program, we wanted to know how often child-specific

utility measures were used in decision making in Australia. Specifically, how many decisions on children's medicines had been made, how many of these involved explicit considerations of quality of life, and how many were informed by child-specific, adult, or through other measures and utilities. We also asked how much the measurement and valuation of HRQoL contributed to uncertainty in decision making for children's medicines.

## Our approach

Recommendations to include medicines on the Australian Pharmaceutical Benefits Scheme (PBS), which provides subsidized access, are made by the Pharmaceutical Benefits Advisory Committee (PBAC) based on evaluation of submissions received from sponsors. The PBAC publishes public summary documents, which are summary versions of each submission and the committee's deliberations, thus providing an excellent resource for our research question. The PBAC provides guidance to sponsors preparing submissions and has a preference for cost-utility analysis, but does not mandate the type of economic evaluation or the choice of HRQoL measures to be used in a cost-utility analysis.<sup>6</sup>

To determine which medicines were relevant for children, we sought information from 4 sources: (1) the World Health Organization (WHO) Model Lists of Essential Medicines for Children, (2) medicines used by children who are part of the Longitudinal Study of Australian Children (LSAC), (3) searches on the PBAC website, and (4) vaccines listed for children on the Australian National Immunisation Program. These sources were then used to develop a list of medicines for children that had been considered by PBAC since the publication of public summary documents commenced. We then determined whether submissions used cost-utility analysis using utility values or QALYs. Next, we categorized the public summary documents into whether the utilities were from child-specific measures, adult measures, or had been directly elicited.

## What we found

There were 1889 submission documents available on the PBAC website from 2005 (when the documents were first available) to when we extracted the data in mid-February 2021). We had sourced 174 medicines used by children from our 4 sources, after duplicates were removed. This resulted in 62 public summary documents from PBAC submissions covering 29 medicines/ vaccines (each medicine may have multiple documents). As shown in **Figure 1**, only 6% of the documents included child-specific HRQoL instruments, 26% used adult, and 18% used direct elicitation. In half the documents, we could not determine the sources of the utility values. The 4 documents for 2 medicines with child-specific measures both used the Health Utility Index Mark 2 (HUI2).<sup>7</sup> Adult instruments used included the EQ-5D,<sup>8</sup> the Assessment of Quality-of-life Questionnaire (AQoL),<sup>9</sup> and 2 used the Asthma Quality of Life Questionnaire 5 Dimensions (AQL-5D).<sup>10</sup> Direct elicitation methods included time trade-off, standard gamble, discrete choice experiment (DCE), willingness to pay, and a vertical rating scale.

Of the 34 medicines that did not include child-specific utilities, we determined that in 85.3% of cases using child-specific utility measures would have reduced or potentially reduced uncertainty in decision making about subsidization of medicines for children (**Table 1**). This determination was made based on: (a) if cost-utility analysis was used in the submission, (b) whether utility values were thought to be sensitive and/or important in the economic model, and (c) whether children were a significant part of the population being considered.

## Child-specific utility measures

Preference-based measures have been developed for child and adolescent populations, such as the AHUM, AQoL-6D, CHU9D, EQ-5D-Y, HUI2/3, QWB, 16D, and 17D<sup>4</sup>; however, the HUI2 was the only measure reported in the PBAC submissions and only for 2 medicines. This may reflect the availability of appropriate preference-based measures being used in the clinical trials, as these form the basis of these submissions.

Utilities are a key input to the economic models that inform value for money,

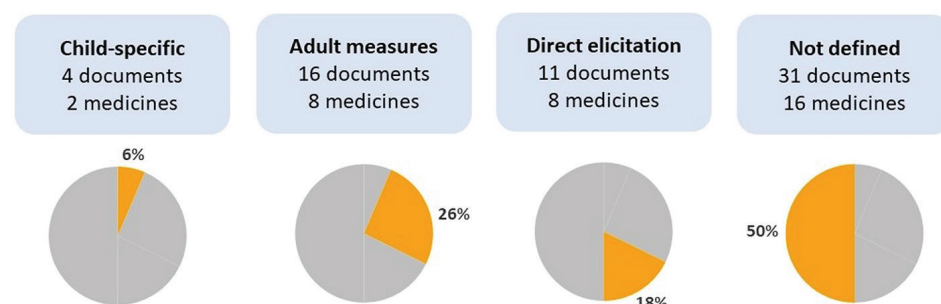
and uncertainty around utility values directly impacts the incremental cost-effectiveness ratio. Child-specific HRQoL instruments have been designed around the domains and descriptors of quality of life that are relevant to children. When used, these instruments should provide greater clarity to decision makers about how the interventions improve patient well-being in the treated population, compared to adult measures.

## Non-child-specific utility measures

The use of adult measures to inform cost utility analysis of interventions for children was considered by the PBAC as not appropriate for children. For instance, in 1 case, the committee commented that “...the EQ-5D instrument was not developed for use in children, and the utilities derived describe the health of the parents of the children in several instances, rather than the health state of the children.”<sup>11</sup>

The use of direct elicitation methods also raised methodological concerns; for example, adults trading off children's lives (Atomoxetine, July 2006), and adults trading off their own lives (pneumococcal polysaccharide conjugate vaccine, November 2010). Direct elicitation techniques may also be focused directly on the specific aspects that the medicine improved without a broader consideration of quality of life; for instance, methods that were aimed at the mode of administration in the case of tobramycin (treatment of cystic fibrosis, March 2013). The committee also observed that vignette wording in these methods may introduce bias; for instance, vignettes for leuporelin (treatment of central precocious puberty, November 2014) used the term “stunted growth.”

**Figure 1. Number of documents and medicines in 4 groups and percentage of documents per group.**



**Table 1. Numbers of medicines where the use of child-specific utility measures may have reduced uncertainty**

	Reduced uncertainty	Potentially reduced uncertainty	Not reduced uncertainty
Adult measures	4	3	1
Direct elicitation	5	3	2
Not specified	8	6	2
<b>Total</b>	<b>17 (50%)</b>	<b>12 (35.3%)</b>	<b>5 (14.7%)</b>

## Uncertainty in decision making

Our finding that the lack of child-specific HRQoL measures increased uncertainty in decision making for medicines used by children highlights an important evidence gap for decision makers. In this review, we found that in almost every instance where patient HRQoL was relied on for a pediatric population, the PBAC did not have child-specific quality of life information or utility values to inform the recommendation.

Because recommendations by PBAC rely on available information, missing information on appropriate utility values is a key source of uncertainty. The consequences of inadequate or missing information about utilities are that the decisions could be based on an inappropriate incremental cost-effectiveness ratio, meaning the government could pay too much for a medicine, or not recommend a medicine, thus potentially delaying access for children and adolescents. Please see our full paper for a more complete outline of how we assessed uncertainty in this context.<sup>1</sup>

**The lack of child-specific HRQoL measures increased uncertainty in decision making for medicines used by children highlights an important evidence gap for decision makers.**

### Future research

Future research directions include improving the evidence on the validity of existing child utility measures, investigation of methods for valuation of child-specific utility measures, and development of value sets for a range of countries. Another critical area is determining measures and valuation methods that are relevant at different ages, especially for younger children. It is also essential to establish the age that an adult instrument may be suitable for adolescents. Other aspects include the inclusion of child-specific instruments in clinical trials, and to develop guidelines and health technology assessment evaluation processes.

### Limitations

The study relied on the information in the public summary documents, but

in half of the documents reviewed, we were unable to determine the source of the utilities. These documents are summaries of the submission and evaluation, and commercial in confidence material (such as drug costs, and incremental cost-effectiveness ratios) is redacted. Further, not all aspects of the submission, including information that may not be commercial in confidence or sensitive, are reported in the documents.

### Conclusions

There is increasing interest internationally on improving the evidence base for reimbursement decision making for healthcare. We now require better evidence about children's health-related quality of life. The use of child-specific instruments was minimal in decision making in Australia, and increased use of such instruments would reduce uncertainty in this process. Our judgment that many of the PBAC's decisions on medicines could have been informed (providing greater certainty) through the use of child-specific instruments of HRQoL suggests that there are significant knowledge gaps about quality-of-life impacts on children.

*Quality Of Life in Kids: Key evidence for decision makers in Australia (QUOKKA) research program aims to strengthen measurement and valuation of pediatric HRQoL. For information and news about our research, follow us on Twitter: @QUOKKA\_Research and check our website: <https://www.quokkaresearchprogram.org>*

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# Medication Management Practices for Noncommunicable Diseases During the COVID-19 Pandemic: A Snapshot of the European Situation

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Our survey highlights differences in the disruption of face-to-face care and in the number of available e-health services during the COVID-19 pandemic across European countries.

A paradigm shift in patient management is warranted to ensure optimal access to healthcare services and pharmacological treatments during COVID-19, as well as possible future pandemics.

## Introduction

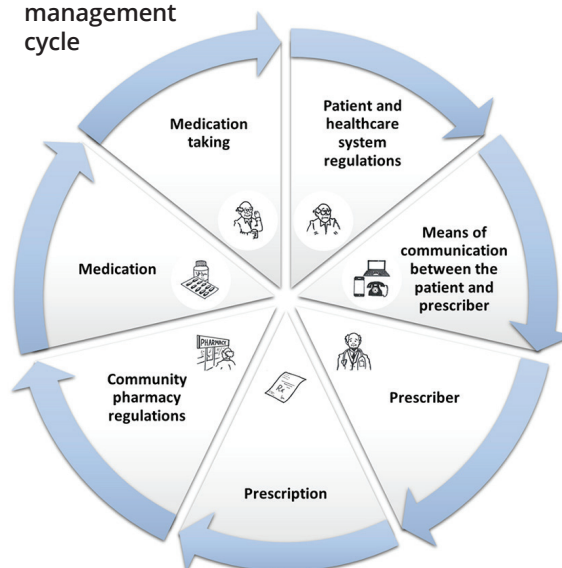
The appropriate management of noncommunicable diseases (NCDs) is important during a pandemic; however, the intensive focus on COVID-19 prevention, the management of patients with COVID-19, and the lockdown and physical distancing restrictions adversely affected NCD-related healthcare services.<sup>1</sup> In May 2020, the World Health Organization surveyed service delivery for NCDs across 155 countries and found that in 75% of countries around the world there was considerable disruption to NCD services due to COVID-19.<sup>1</sup> Across services, rehabilitation was the most impacted, with 79% of countries in Europe reporting disruption to rehabilitation services.<sup>1</sup>

The continuity of medication therapy is a cornerstone for the effective management of NCDs.<sup>2</sup> Even before the COVID-19 pandemic, about 50% of people with NCDs were nonadherent to their medication,<sup>3</sup> which can have potentially serious negative consequences on their

health outcomes (eg, increased risk for cardiovascular events).<sup>4</sup> Continuous access to medication is a prerequisite for appropriate treatment adherence, which disruptions of healthcare services may compromise due to COVID-19.

The European Network to Advance Best Practices & Technology on Medication Adherence (ENABLE; CA19132), launched in October 2020, is a 4-year research initiative funded by the European Commission under the COST Action program.<sup>5</sup> Among others, ENABLE aims to evaluate current practices related to medication management (Figure 1). Given increasing concerns that patients with NCDs may not be receiving appropriate care or access to their medication during the COVID-19 pandemic<sup>1</sup>, ENABLE considered it important to assess the medication management practices in place for NCDs during the COVID-19 pandemic across European countries and to evaluate its association with the population burden of COVID-19 and country income.

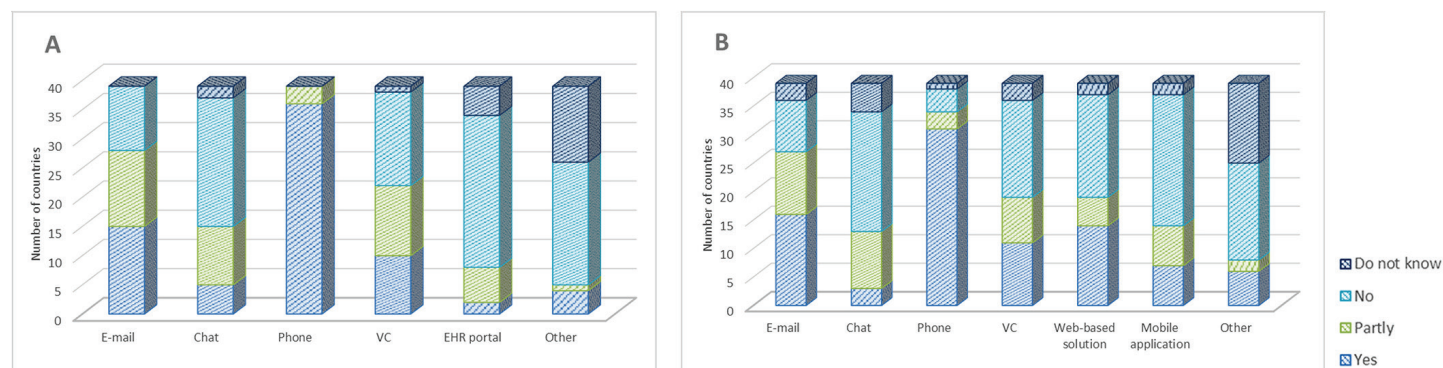
**Figure 1. Medication management cycle**



## Survey on medication management practices during the COVID-19 pandemic

In December 2020, ENABLE conducted a cross-sectional, web-based survey in 38 European countries and Israel on available medication management services for NCDs. A 33-item, English language questionnaire was developed based upon 7 domains of the NCDs medication management cycle defined by ENABLE working group (Figure 1). Descriptive statistics, non-parametric tests, and generalized linear models were applied to analyze the data. The population burden of COVID-19 was defined in line with the European Centre for Disease Prevention and Control as the number

**Figure 2. Availability of various forms of e-health services for symptom monitoring and patient management (A), and teleconsultation modalities for requesting chronic medication prescriptions (B)**



EHR indicates electronic health record; VC, videoconsultation.

of COVID-19 cases and COVID-19 deaths per 100,000 inhabitants<sup>6</sup> and country income was assessed as gross domestic product per capita (GDP/capita) at purchasing power parity.<sup>7</sup> This survey was reported according to the Checklist for Reporting Results of Internet E-Surveys (CHERRIES).<sup>8</sup> A more detailed description of the methodology is described elsewhere.<sup>9</sup>

From the 92 invited ENABLE collaborators, 53 experts (ie, healthcare providers and academics with medical or pharmaceutical backgrounds) from all 39 target countries completed the survey. In 35 (90%) of the evaluated countries, there were disruptions to face-to-face consultations in primary care and/or outpatient clinics due to

per 100,000 inhabitants. In the evaluated 39 countries, the mean±SD number of available e-health services for symptom monitoring and patient management (eg, e-mail, online chat, phone, videoconference, electronic health record portal, or other) and teleconsultation methods for requesting prescriptions for chronic medications (eg, e-mail, online chat, phone, videoconference, web-based solution, mobile application, or other) was 3±1.3 and 3.4±1.6, respectively. The mean±SD number of available e-health services for the management of NCDs showed a trend to be lower in upper/middle (2.1±1.1) compared to high income countries (3.2±1.3;  $P=.05$ ). In contrast, the number of available teleconsultation methods for requesting prescriptions did not correlate with country income (upper/middle income countries: 2.9±1.6 versus high income countries: 3.5±1.6). The available forms of e-health services and options for requesting medication prescriptions were different across European countries. In most countries, phone and e-mail were the most commonly available modes of teleconsultations between patients and physicians during the pandemic in December 2020 (Figure 2). However, in countries with higher GDP per capita, a more comprehensive range of e-health services (eg, online chat, video consultations, communication via the electronic health record portal, alerts when prescriptions need to be renewed, online ordering of prescription medication) were available for patients with NCDs.

Our survey highlights differences in the availability of face-to-face services and

the number of e-health services during the pandemic across European countries. Further large-scale studies are warranted to better understand the long-term clinical and economic consequences of the considerable disruption of face-to-face NCD services due to COVID-19 and to validate the trends observed in this study (ie, the association between the disruption to face-to-face healthcare services and the number of COVID-19 deaths per 100,000 inhabitants and between the number of available e-health services for the management of NCDs and country income).

Based on our findings, several practical solutions could be suggested to ensure access to NCD treatments during the pandemic, including:

- an increased range of remote services for ordering repeat prescriptions (eg, online, via mobile app),
- expanding the scope of professionals authorized to prescribe medications (or issue repeat prescriptions) via e-health services,
- increasing the duration of prescriptions (although this needs to be balanced with managing shortages and whether appropriate given the medication and the disease),
- allowing substitution of unavailable drugs (should consider existing comorbidities and comedication),
- creating e-health systems supporting patients in long-term treatment, encouraging patient empowerment and patient-centered care, and
- providing publicly available guidance on strategies for maintaining treatment during the pandemic lockdown.<sup>10</sup>

**Continuous access to medication is a prerequisite for appropriate treatment adherence, which disruptions of healthcare services may compromise due to COVID-19.**

the COVID-19 pandemic. Disruption to face-to-face healthcare services showed a positive association with the number of COVID-19 cases (mean±SD in countries with “yes,” “partly,” and “no” disruption: 3655.1±1561.9, 4580.4±1818.9, and 1772.9±712.5;  $p=0.03$ ) and a positive trend with the number of COVID-19 deaths (mean±SD in countries with “yes,” “partly,” and “no” disruption: 73.2±41.9, 82±37.7, and 23±17;  $P=.05$

Our results should be considered in light of certain limitations. The self-developed questionnaire and multiple-choice questions with closed answers allowed us to seek precise information; however, it may be biased as the questionnaire was available only in English and was not

**Disparities in the availability of face-to-face services and the number of e-health services in the management of patients with NCDs points to the need for a paradigm shift to optimize access to healthcare services and treatments during the COVID-19 pandemic and beyond.**

translated to the native language of the participants. The survey was conducted among ENABLE collaborators whose views represent one perspective only and cannot be considered representative. It is also important to highlight that in this survey only the availability of healthcare services was assessed, but data on healthcare resource utilization were not collected. Finally, this survey represents

the situation in December 2020, and findings may have differed substantially if the survey had been distributed at another time.

### Conclusions

The COVID-19 pandemic limited the number of face-to-face appointments in patient care; however, e-health modalities for managing NCD patients were available in many European countries. Disruption to face-to-face consultations was associated with a greater population burden of COVID-19 and the number of available e-health services was associated with higher country income. Disparities in the availability of face-to-face services and the number of e-health services in the management of patients with NCDs points to the need for a paradigm shift to optimize access to healthcare services and treatments during the COVID-19 pandemic and beyond.

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# Characterizing the Occurrence of Stroke in Long COVID: How Can We Assess This Evolving Topic?

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There is a paucity of evidence that assesses the relationship between long COVID and the onset of stroke, particularly in patients in recovery from critical care.

Much of the literature concluded that cerebrovascular complications may occur in patients with long COVID after being hospitalized for severe COVID infection.

Given the insufficiency of published evidence measuring stroke-related outcomes in long COVID, we further reviewed treatment guidelines to corroborate the issues that we had previously observed in the coronavirus literature.

There is an urgent need to synthesize emerging evidence regularly and systematically from ongoing and future global trials to document how the management of long COVID may evolve over time.

The past 2 years of public health surveillance have shown that complications from SARS-CoV-2 infection are not limited to the respiratory system, with some patients presenting with cerebrovascular disease and stroke.<sup>1,2</sup> Available data indicate that most patients hospitalized due to severe COVID-19 infection consequently have other neurological complaints related to the brain or nervous system. A severe infection increases the risk of vascular damage and cerebrovascular complications, which are more likely to occur in patients who were critically ill and hospitalized.<sup>1</sup>

**Our review identified multiple confounders that impacted our ability to assess the relationship between long COVID and the onset of stroke.**

Postacute COVID-19 syndrome, known as “long COVID,” describes lingering complications that extend  $\geq 4$  weeks beyond the initial symptoms of COVID-19.<sup>2</sup> This is an evolving topic of interest for the health economics and outcomes research (HEOR) community, as it impacts health policy and strains health resources.<sup>3</sup> Despite 2 years’ worth of published biomedical literature from the COVID-19 pandemic at our disposal, there is a paucity of evidence that assesses the relationship between long COVID and the onset of stroke, particularly in patients in recovery from critical care. Stroke is often reported as a major adverse cardiovascular event; however, it was classified as a neurological disease in 2017,<sup>4</sup> and thus may be categorized as a neurological complication in long COVID.

A systematic literature review is an essential component in evidence-based practice and ensures that all outcomes of interest are pooled and appraised

to answer a research question. We conducted this systematic literature review to identify studies reporting stroke-related outcomes in patients suffering from long COVID who were previously hospitalized for a severe COVID-19 infection to assess how these outcomes have been reported and whether there is an increased risk of stroke in this patient group.

The systematic literature review was performed in accordance with the Cochrane and PRISMA guidelines and consolidated the findings of relevant peer-reviewed research published between January 2020–June 2021 into a conference proceeding for an ISPOR conference, which was published in *Value in Health*.<sup>5</sup> The review was subsequently updated in January 2022 for this *Value & Outcomes Spotlight* article. Biomedical literature databases, among other sources (eg, conference proceedings from stroke journals, COVID-19–related guidelines and web sources, active/recruiting clinical trials) were searched.

Studies reporting patients with long COVID (ie, diagnosed  $\geq 4$  weeks after initial infection and discharged from critical care), were appraised with no restriction by country/region. Outcomes including secondary cerebrovascular events and stroke characteristics were of interest.

## Large-scale studies on long COVID rarely include stroke-related outcomes

Of the 5628 publications that were assessed in the systematic literature review, a total of 4 published studies (2 medical chart reviews and 2 prospective observational studies) and 4 ongoing clinical trials were found relevant in the original 2021 review. An additional 3 retrospective cohort studies and 2 interventional trials were identified in the 2022 update. Studies were conducted in Europe, India, Iran, Ukraine, and the United States, and measured a range of stroke-related outcomes from the onset



of long COVID up to 92 days' follow-up. The study designs, along with the reporting of cerebrovascular events and neurological complaints, were variable. Therefore, the evidence was not suitable for quantitative analysis. The incidence of stroke post-discharge ranged from 0.45% (United States) to 11.5% (Ukraine). The onset of thrombosis occurring after hospital discharge ranged from 1.61% to 2.5% in the United States, with only 1 study reporting arterial thromboembolism (0.7%). A single study reported the mortality due to stroke at 0.59% (Iran) and another study measured a composite outcome of cerebrovascular events.

Overall, our review identified a dearth of peer-reviewed literature that had measured stroke-related outcomes at timepoints associated with long COVID. We found clear discrepancies in the definition of long COVID, for example, in studies measuring stroke-related outcomes <4 weeks from a severe COVID-19 infection. This

timepoint is in contrast to the World Health Organization's definition of long COVID (ie, complications extending  $\geq 4$  weeks beyond initial symptoms)<sup>6</sup> that we adopted as an inclusion criterion. Consequently, much of the literature was deemed ineligible during the review process.

**A deeper understanding of the postacute COVID-19 pathogenesis and a wider, more homogenous evidence base are required to assess whether there is any clinically significant relationship between long COVID and stroke.**

The identification of evidence gaps by a rigorous systematic literature review process can influence the practice of evidence-based medicine and drive

decision making. Our review identified multiple confounders that impacted our ability to assess the relationship between long COVID and the onset of stroke, including anticoagulation treatment given to hospitalized patients with a severe infection, unclear etiological factors of stroke, and disruption to global clinical trials. Further, few studies stratified stroke outcome data by ethnicity or age group, which has also been discussed in a separate published living systematic review on long COVID.<sup>7</sup>

Despite the variation in study methodology, much of the literature concluded that cerebrovascular complications *may* occur in patients with long COVID after being hospitalized for severe COVID infection, albeit at very low rates. With the limited evidence, there are no comparative data available versus the general population. In 3 of 4 studies that commented on the efficacy of administering prophylactic medication to prevent cerebrovascular complications posthospital discharge, authors

**Table 1: Ongoing studies measuring stroke-related clinical outcomes in patients with long COVID**

Study details	Study title	Outcomes measured	Estimated study completion date
OPTIC-19 (NCT04838106) England, Wales	Outcomes of patients who survived treatment on an intensive care unit for COVID-19 in England and Wales (OPTIC-19)	Emergency hospital admission for a major adverse cardiac event (MI, stroke, heart failure)	July 31, 2022
NCT04650087 United States	COVID-19 thrombosis prevention trials: posthospital thromboprophylaxis	Composite outcome of symptomatic DVT, PE, other venous thromboembolism, ischemic stroke, other ATE, and all-cause mortality at 45 and 90 days after hospital discharge. New, symptomatic ATE (inclusive of stroke, MI, or peripheral arterial thromboembolism) at 30 days	August 2022
CORONA-VTE NET (NCT04535128) United States	COVID-19 registry to assess frequency, risk factors, management, and outcomes of arterial and venous thromboembolic complications	30-day and 90-day frequencies of arterial (MI, stroke, or systemic embolism) and venous thromboembolic events	December 31, 2022
ACTIV4 Registry (NCT05226416) Russia	Analysis of health status of comorbid adult patients with COVID-19 hospitalized in fourth wave of SARS-CoV-2 infection (ACTIV4)	Death for any cause, including stroke, from date of hospitalization until date of first documented date of death, assessed up to 12 months. Onset of any disease, including stroke, at 3, 6, 12 months postdischarge	February 2023
unCOVER-AF (NCT04830774) United States, Belgium, Italy	Natural history of COVID-19-related AF (unCOVER-AF)	Composite of all-cause mortality, stroke, and bleeding at 3 years. Time to ischemic stroke within 3 years	December 31, 2023
CV-COVID-19 (NCT04359927) Spain, Italy	Long-term effects of coronavirus disease 2019 on the cardiovascular system, CV COVID registry: a structured summary of a study protocol	Stroke rate at 1 year defined according to the Academic Research Consortium-2	

*ACTIV4 indicates Analysis of health status of comorbid adult patients with COVID-19 hospitalized in fourth wave of SARS-CoV-2 infection; AF, atrial fibrillation; ATE, arterial thromboembolism; CORONA-VTE NET, COVID-19 registry to assess frequency, risk factors, management, and outcomes of arterial and venous thromboembolic complications; COVID-19, coronavirus disease 2019; CV, cardiovascular; DVT, deep vein thrombosis; MI, myocardial infarction; NCT, the National Clinical Trial Number; PE, pulmonary embolism.*

suggested that extended prophylaxis may not incur a net clinical benefit. We call for good-quality randomized data to: (i) measure the incidence of stroke-related outcomes in long COVID in a controlled manner, and to (ii) inform recommendations for universal post-discharge prophylaxis.

Further, we eagerly await data from planned European and US long COVID studies that intend to measure cerebrovascular-related outcomes as a primary or secondary endpoint by a future completion date (Table 1).

### Management of long COVID and stroke-related neurological complications are not clearly defined in the available treatment guidelines

Given the insufficiency of published evidence measuring stroke-related outcomes in long COVID, we further reviewed treatment guidelines in this indication to check if any observed heterogeneity between clinical guidelines would corroborate some of the issues that we had previously observed in the coronavirus literature.

**Figure 1** summarizes the available clinical guidelines and recommendations for patients with postacute COVID-19 for each stage of care, according to a mapped patient journey. Similar to our systematic literature review findings, the following points were concluded:

- Clinical guidelines inconsistently defined long COVID, with some guidelines suggesting that the definition will continue to evolve
- Some guidelines recommend prophylactic anticoagulation treatments to be prescribed for hospitalized patients with acute COVID-19 who are without any contraindication or need for higher dosage<sup>8,9</sup>
- Prophylactic anticoagulation treatments at hospital discharge were generally not recommended in the guidelines
- Many guidelines offered advice for all-cause complications in postacute COVID/long COVID, but there were limited specific recommendations for neurological complications including stroke

Taken together, the guidelines consider supportive management, symptom monitoring, and educating the patient on when to seek emergency care following hospital discharge. The National Institute for Health and Care Excellence recommends monitoring for “symptom alerts” of long COVID that occur within 1 to 2 weeks,<sup>10</sup> and the Scottish Intercollegiate Guidelines Network recommends this at 6 weeks postdischarge.<sup>11</sup>

### Conclusion

As interest in long COVID continues to evolve, future research may help us determine the true burden of stroke in long COVID. Although there are several published studies on postacute COVID-19, many large regional and global longitudinal follow-up studies have not included stroke outcomes in their scope. Even when they did, the stroke-related outcomes were not clearly stratified by the timepoints of occurrence (ie, whether these were since a severe infection or hospitalization).

A deeper understanding of the post-acute COVID-19 pathogenesis and a wider, more homogenous evidence base are required to assess whether there is any clinically significant relationship between long COVID and stroke. The systematic literature review process represents unbiased, high-quality evidence using robust methodologies that often drive clinical practice. The current systematic literature review highlights the possibility of cerebrovascular consequences of long COVID after a severe COVID-19 infection and is in contrast to other published systematic literature reviews that focus on cerebrovascular complications during a severe COVID-19 infection. Such evidence will presumably lead to clinical research with stroke-related endpoints, which will be essential to manage future pandemics of such magnitude.

**Figure 1: Summary of guidelines and recommendations for patients with postacute COVID-19**

PATIENT JOURNEY							
	Guideline on use of prophylactic anticoagulation in hospitalized patients	Management of hospitalized patients with rapid neurological deterioration	Guidelines on postdischarge anticoagulation or thromboprophylaxis treatment	Guideline on the definition of PACS	Guideline on management of any complication of PACS	Guideline on management of neurological or cognitive complications in PACS	Guideline on management of stroke complications in PACS
NIH	✓	✓	✓	✓	✓		
CDC				✓	✓	✓	
Nuffield Department of Primary Care Health Sciences, UK			✓	✓	✓	✓	✓
BMJ					✓		
WHO	✓		✓	✓	✓	✓	✓
NICE	✓			✓	✓	✓	
SIGN	✓				✓		

BMJ indicates British Medical Journal; CDC, Centers for Disease Control and Prevention; NICE, the National Institute for Health and Care Excellence; NIH, the National Institutes of Health; PACS, postacute COVID-19 syndrome; SIGN, Scottish Intercollegiate Guidelines Network; WHO, World Health Organization.

At present, we feel that this assessment is hindered by limitations of the literature. Our findings call for prospective, robust, controlled trials that evaluate the cerebrovascular consequences of long COVID after a severe acute COVID-19 infection. Because the effects of the pandemic will be felt for years to come, there is an urgent need to synthesize emerging evidence regularly and systematically from ongoing and future global trials to document how the management of long COVID may evolve over time.

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# Guiding Principles for Using Clinical Outcomes Assessments in Real-World Studies: What to Do When There Is No Regulatory Guidance

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When clinical outcomes assessments (COAs) are used in real-world studies to measure patient-reported endpoints, a robust study design that guides the selection, analysis, interpretation, and integration of COA data is critical to ensure the data are valid, meaningful, fit-for-purpose, and high-quality.

To more accurately use COAs in real-world studies, the available randomized controlled trial guidance for the use of COA data needs to be adapted to meet the challenges of studies carried out in the real-world context.

Truly reflecting the patient's voice in real-world evidence is important not only because these data can be considered for regulatory decision making, but can also better translate into improved care targeted at patients' needs and priorities.

## Introduction

Real-world data (RWD) and real-world evidence (RWE) are increasingly important in healthcare decision making. Medical product developers generate RWD and RWE to support and add value to their randomized clinical trial (RCT) findings (eg, via data captured in electronic health records, patient-generated data from surveys, wearables, mobile devices, etc, and from healthcare claims and disease registries).

Real-world studies can be used to generate insights that contextualize and generalize the findings from clinical trials where participants are selected by strict inclusion/exclusion criteria. Regulatory agencies and reimbursement authorities also use RWD and RWE to monitor the efficacy, safety, and cost-effectiveness of novel products. Well-designed real-world studies can provide additional evidence for clinical effectiveness and safety for patients under an array of heterogeneous conditions, as well as demonstrate the patient-relevant value of new products to end users (ie, patients, carers, physicians, and payers).

A clinical outcome assessment (COA) is a clinical evaluation instrument that is used to measure patient outcomes in a clinical trial. There are 4 types of COAs: patient-reported outcomes, clinician-reported outcomes, observer-reported outcomes, and performance-based outcomes assessments.

However, there are limitations to incorporating the patients' voice obtained from RWE data into clinical and regulatory decision making due to lack of standardization among real-world studies. Real-world prospective studies are designed to reflect clinical experience across a broader and more diverse distribution of patients than an RCT and use the same COAs developed in trials. This is because many prospective real-world studies seek to provide a line of complementary evidence to that of an RCT.

Nonetheless, this approach can become problematic given the current practices surrounding the implementation and interpretation of COA data are variable, particularly in real-world practice whereby data are collected outside of the constraints of the RCT. While some studies are designed robustly with clear study hypotheses and research objectives using validated COAs to derive data, other studies are carried out without the inclusion of validated or reliable COAs, leading to questionable and ambiguous study findings. When COAs are used in real-world studies to measure patient-reported endpoints, a robust study design is critical to ensure the appropriate use and application of COAs and patient-relevant data analysis for high-quality real-world study findings.

**Well-designed real-world studies can provide additional evidence for clinical effectiveness and safety for patients under an array of heterogeneous conditions, as well as demonstrate the patient-relevant value of new products to end users (ie, patients, carers, physicians, and payers).**

To date, there is no regulatory or health technology appraisal guidance or publications pertaining to the standardization of COA usage in real-world studies. This differs from clinical trials. The US Food and Drug Administration (FDA) has produced guidance on patient-focused drug development<sup>1,2</sup> and patient-reported outcomes in the seminal 2009 Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.<sup>3</sup> ISPOR has supplemented the 2009 guidance publishing 12 ISPOR Good



Practices Reports (**Table 1**) that provide additional detail for trial conduct for medical label claims.<sup>4-15</sup>

In addition, the European Medicines Agency has published guidance on the incorporation of COAs (again, in this case on patient-reported outcomes<sup>16</sup>) as a measure of treatment efficacy in clinical trials. Finally, other organizations, such as the CONSORT consortium, are working

on standardization of COA use in clinical trials.<sup>17</sup>

While the existing guidance sets a high precedent in terms of study design, guidance documents were written in the context of regulatory approvals or with a specific purpose for RCTs. These types of guidance may fail to address the nuances that arise in studies carried out in the real-world setting. This is problematic

because if we are to truly capture the patient voice using COA in real-world studies, guidance needs to address the particularities of COAs data outside RCTs, including heterogeneous patient samples, biases potentially created by open-label use, data collection practices, etc, that do not reflect common clinical practice or the impact of different study settings.

The ISPOR COA SIG's Member Engagement Working Group undertook an ISPOR-wide survey project to determine the importance of guidance on incorporating COAs into real-world studies. The survey's primary objective was to determine interest in (1) best practices for the design, use, and analysis of COA data in real-world studies, (2) methods for operationalization of COAs in real-world studies, and (3) regulatory guidance for the use of COAs in real-world studies.

With the survey's findings, the working group developed a thought-provoking roundtable discussion, "Guiding Principles for Using COAs in Real-World Studies" to discuss the challenges in conducting these studies and potential solutions. The panelists discussed 4 primary concerns with the current use of COAs in real-world studies and proposed corresponding solutions, especially when compared to the use of COAs in clinical trials (**Table 2**).

The first concern was a lack of transparency about study design in real-world studies when compared with the transparency in clinical trials. For instance, many real-world studies develop stand-alone questions for use in a study rather than searching for and using existing and validated COAs.

A potential solution proposed was the creation of decision panels for specific therapeutic areas with the purpose of recommending appropriate validated COAs within each context of use. This could generate a known set of COAs, which could be used across studies to allow for greater consistency in study design, which could then facilitate comparison between studies. Emphasis should be made on the importance of interdisciplinary collaborations, where patient-centricity/COA specialists should be involved in outcomes decision

**Table 1. ISPOR's 12 PRO and COA Good Practices Reports**

Published ISPOR PRO and COA Good Practices Reports	
1.	Translation and Cultural Adaptation Process for PRO measures (2005*)
2.	Translation and Linguistic Validation of PRO Instruments (2009†)
3.	Measurement Equivalence Between Electronic and Paper-Based PRO Measures (2009)
4.	Content Validity in Existing PRO Instruments and Their Modification (2009)
5.	Content Validity in Newly Developed PRO Instruments Part 1—Eliciting Concepts for a New PRO Instrument (2011)
6.	Content Validity in Newly Developed PRO Instruments Part 2—Assessing Respondent Understanding (2011)
7.	ePRO Systems Validation (2013)
8.	Assessment of PROs in Children and Adolescents (2013)
9.	Mixed Modes to Collect PRO Data in Clinical Trials (2014)
10.	Clinical Outcome Assessments: A Conceptual Foundation (2015)
11.	Clinician-Reported Outcomes Good Measurement Practices (2017)
12.	PRO and Observer Reported Outcomes Assessment in Rare Disease Clinical Trials (2017)
Upcoming ISPOR PRO and COA Good Practices Reports	
Measurement Comparability of PROMs	
• Publication in <i>Value in Health</i> expected in 2023	
• This report will update #3 & #9 reports	
Performance-Based Outcomes Assessments—Part 1: Introduction	
• Publication in <i>Value in Health</i> expected in 2023	

\* Landmark methodology report: Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes Measures: Report of the ISPOR Task Force for Translation and Cultural Adaptation.

† All reports published from 2009 onward are based on FDA's PRO Guidance for Industry, 2009.

COA indicates clinical outcomes assessment; ePRO, electronic patient-reported outcome; FDA, US Food and Drug Administration; PRO, patient-reported outcome; PROMs, patient-reported outcomes measures.

**Table 2. Identified concerns with clinical outcome assessment use in real-world studies**

1.	Lack of transparency about study design in real-world studies
2.	Analysis of clinical outcomes assessment data in real-world studies, specifically a lack of a priori planning
3.	Missing data mitigation
4.	Current guidelines (real-world-specific and clinical outcomes assessment-specific) do not sufficiently cover use of clinical outcomes assessments in a real-world context

making, analyses, interpretations, and education throughout the product evidence life cycle.

The second issue raised was around the analysis of COA data in real-world studies, specifically a lack of a priori planning. Panelists emphasized the need to justify the selection of the COA at the *beginning* of the study and then *prespecify* the endpoints to be analyzed, especially given that many COAs can generate multiple endpoints. This justification should include the reasons for the scoring algorithm, including the domain score, as well as the total scores of the COAs.

**There was consensus that there needs to be more rigor in the selection, implementation, and analysis of COAs in real-world studies.**

A third concern was around mitigating missing data, which tends to be a concern in real-world studies because of the inability to impose study visits or data capture when it is not routine practice, resulting in less monitoring of data capture. It was proposed that at the outset attention should be paid to questionnaire length and the order of questions because missing data often occur on the last few questions so responses that may derive a primary or key secondary endpoint should be queried first. A further suggestion to minimize missing data was use of electronic data capture whenever possible.

The final problem discussed was the fact that current guidelines (eg, Framework for FDA's Real-World Evidence Program) do not sufficiently cover use of COAs in a real-world context. For instance, patients are unblinded to treatment in real-world studies, which raises the concern of bias in their answers. Furthermore, real-world studies can report on data from multiple stakeholders, including international collaboration that can bring in issues of data governance.

Generally, it was agreed that real-world studies would benefit from the use

of existing FDA guidance documents for the use of COAs in clinical trials.<sup>1-3</sup> Additionally, it was suggested that COAs developed in accordance with the best practices outlined in the 2009 FDA guidance should be considered during the study design phase for use in real-world studies, although adaptations may be needed. There was consensus that there needs to be more rigor in the selection, implementation, and analysis of COAs in real-world studies.

The findings from the survey and roundtable discussion demonstrate the need for guidance to standardize the current variable approaches. The development of emerging good practices for COAs in real-world studies like the previously mentioned ISPOR Good Practices Reports would be a step in the right direction. The refinement and standardization of current practices will ultimately lead to more robust, patient-relevant data generated from real-world studies that are invaluable to the multiple stakeholders involved in healthcare decision making.

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## Addressing the Evidence Gap in Evaluating the Health of Children

An Interview with Wendy J. Ungar, MSc, PhD

Section Editor: Marisa Santos, PhD, MD, Instituto Nacional de Cardiologia, Rio de Janeiro, Brazil



Photo courtesy of Wendy J. Ungar

# Q&A

“Agencies that produce guidelines around the world must further explicitly recognize the methodologic challenges in conducting economic evaluations in child health and provide guidance on alternative approaches.”

*This month, I had the pleasure of interviewing Wendy J. Ungar, MSc, PhD, for Value & Outcomes Spotlight's theme that focuses on the valuation of health in children. Dr Ungar is a Senior Scientist in the Child Health Evaluative Sciences Department at the Hospital for Sick Children Research Institute and Professor at the Institute of Health Policy, Management and Evaluation at the University of Toronto in Canada. She holds the Canada Research Chair in Economic Evaluation and Technology Assessment in Child Health. In 2007 she founded [TASK \(Technology Assessment at Sick Kids\)](#), where she and her team conduct research applying health economic methods to child health and are responsible for maintaining the [PEDE database](#), a user-friendly online database of pediatric economic evaluations published since 1980, used by health technology assessment agencies around the world. Her book, [Economic Evaluation in Child Health](#), was published by Oxford University Press in 2010.*

**VOS:** Developing health economic models for children is a challenge. Can you discuss some of the major roadblocks you face in your work?

**Wendy Ungar:** When conducting economic evaluations in children, it's not simply a matter of including age as a variable. Differences between child and adult health must be recognized in terms of developmental vulnerability, dependency, unique patterns of health resource use, and unique patterns of morbidity and mortality. These aspects must be considered when designing an economic evaluation in child health. Key challenges to conducting these studies include:

- The inability to measure preferences for health states in infants, toddlers, and very young children, and reliance on proxies
- The need to consider changes in resource use and health state preferences for different age groups as children mature (ie, neonates, infants, toddlers, school children, adolescents)
- Modeling costs and health consequences over the lifetime
- Using different approaches or instruments for generating utilities in different age groups
- Effects of discount rates when upfront costs are high and benefits are deferred or accrue over many decades
- The need to incorporate the costs and consequences of spillover effects on caregivers and family members



**VOS:** At what age do you believe a child can begin to complete a multi-attribute instrument?

**WU:** A major problem is that most preference-based instruments used for indirect elicitation of utilities are implicitly designed for adults. They include quality-of-life attributes that are meaningful to adults but not necessarily relevant for children. They may also have used adults to derive the underlying utility weights. There are some instruments, such as the HUI, CHU-9D, and EQ-5D-Y, that are attracting attention for use in children. However, their classification systems may or may not reflect attributes relevant to child health. Furthermore, children may not have been used to establish underlying utility weights. Even with these child-centric instruments, children younger than 8 years of age typically cannot self-assess and a proxy is needed to provide the responses.

**VOS:** What are the potential drawbacks of utilizing adult proxy replacements to fill instruments?

**WU:** While adults (most often a parent) are accurate reporters for a child's resource use, their proxy responses for dimensions of quality of life have been found to be poorly correlated with a child's responses in many studies. Parents are better reporters for observable attributes such as physical activity and worse reporters for more abstract attributes related to mood and cognition. Parents may also imbue their proxy responses with their own subjective perceptions of their child's health state. Proxy responses should not be pooled with self-assessed responses when calculating utility weights.

**VOS:** How can you build economic models when you don't have any data from generic instruments like the EQ-5D?

**WU:** Like all model building, it's a question of weighing uncertainty against the demand for evidence needed to inform funding recommendations. Health technology assessments (HTAs) and economic evaluations in child health can use cost-effectiveness analysis with natural health outcomes in addition to or instead of a cost-utility analysis when quality of life-years (QALYs) cannot be generated. They may also utilize shorter time horizons. HTA agencies require guidance on alternative modeling approaches and how to evaluate health economic evidence in children when QALYs cannot be generated. Guideline producers must update their guidelines to explicitly consider the methodologic challenges of performing economic evaluations in child health.

**VOS:** Can you name some study evidence gaps for preference-based measures of children's health?

**WU:** As QALYs cannot be validly or reliably generated for infants, toddlers, and very young children (under 6 years of age), this constitutes a major evidence gap. In addition, sound lifetime models for many chronic childhood conditions are lacking. Few health economic evaluations in child health include a societal perspective, which is essential to capture spillover effects such as caregiver productivity losses and caregiving-related QALY losses. Promising research is ongoing to expand the methods used to generate

health state utilities for pediatric conditions, such as the use of parent-child dyad elicitation and discrete choice experiments, as well as methods that circumvent the need for these instruments or cost-utility analyses entirely (ie, willingness-to-pay) via discrete choice experiments and net benefit approaches.

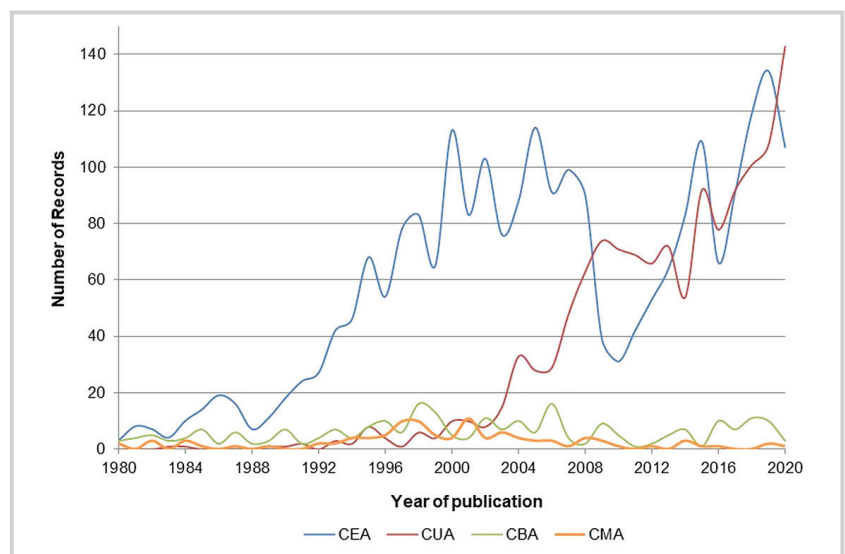
**VOS:** Should QALY gains by children and adolescents, as compared to adults, have different values or carry more weight, in your opinion?

**WU:** This is a great question. Many clinical and funding decision-making bodies inherently value health improvements in children highly as a reflection of altruistic societal beliefs that aim to protect the most vulnerable. This has been borne out by numerous stated preference studies revealing that individuals place greater weight on health improvements in children. This can be difficult to operationalize in cost-utility analyses however, especially given what is stated above with regard to our ability to generate valid QALYs in children. The National Institute for Health and Care Excellence in the United Kingdom has done the most work in this area, examining alternative willingness-to-pay thresholds that may favor investments for more vulnerable populations. Another approach is to rely on the multidisciplinary HTA framework used for funding decision making that places as much (or more) weight on the social, legal, and ethical implications of a particular funding decision, as the incremental cost-effectiveness ratio. Further, many HTA agencies engage directly with patients, families, and members of the public so that their values and preferences regarding the population expected to benefit are directly considered in the funding deliberation.

**VOS:** Are there any specific best practices or challenges to your country/region that you would like to share that may benefit readers?

**WU:** The second Washington panel updated their guidelines in 2016 to include a societal perspective in the reference case and to explicitly recommend inclusion of caregiver productivity

**Figure: Distribution of economic evaluations in PEDE by year (n = 4056)**



Source: <http://pede.ccb.sickkids.ca/pede/index.jsp>

CBA indicates cost-benefit analysis; CEA, cost-effectiveness analysis; CMA, cost-minimization analysis; CUA, cost-utility analysis.

costs as well as costs occurring outside the health sector (ie, education and social and community services), which commonly offer programs that benefit children. Agencies that produce guidelines around the world must further explicitly recognize the methodologic challenges in conducting economic evaluations in child health and provide guidance on alternative approaches.

**VOS:** Is there any other topic or issue related to health-related quality of life in children that you would like to highlight for our readers?

**WU:** The news is not all bad! The volume of published pediatric cost-utility analyses, as indexed in our [PEDE database](#), has grown on average by 23% annually since 2003. In 2020, cost-utility analysis was the most common analytic technique in child health economic evaluation (**Figure**).

More and more health economic researchers are attracted to the field of child health and exciting research is ongoing, examining alternative methods to generate health state utilities, model building, and capturing spillover costs and consequences. For further reading, see the suggested bibliography below.

### **Suggested Bibliography**

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