SHARED RISKS, SHARED BENEFITS: INNOVATIVE PRICING IN HEALTHCARE
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**Q & A**


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.
The COVID-19 pandemic continues to wreak havoc on the world, claiming hundreds of thousands of lives, placing healthcare systems and front-line caregivers under intense strain, and producing economic ruin along the way. What started as a mad scramble to mitigate disease transmission via hand washing, social distancing, and self-isolation, in the hopes that these efforts would be short-lived and our sense of normalcy quickly restored, has gradually given way to the sobering realization that none of this will be short in duration and an as yet to be defined “new normal” lies ahead.

In the meantime, life goes on and adjustments are made. ISPOR is an organization that was founded to bring like-minded people together to discuss all aspects of value and affordability in healthcare. But in a time in which conventional notions of “bringing people together” are impracticable, adjustments are made and so our Society recently convened its first fully remote, digitally enabled conference, called “Virtual ISPOR 2020.”

And you know what? It was amazingly good! The conference experience was completely transformed—what was lost in terms of in-person interaction was offset by some exciting new surprises, such as the ability to view all the sessions (even those running in parallel) and the opportunity to engage presenters in questions and answers in real time. As always, the scientific content was top notch.

Value & Outcomes Spotlight continues to adjust as well. Part of our “new normal” is that we are recognizing that the pandemic impacts pretty much everything in the health sector, including the conduct of health economics and outcomes research. So, we are looking to provide a COVID-19 overlay on each of our themes to bring the topic into sharper focus for present day circumstances. This issue’s theme is innovative pricing models and our feature article lays out the fundamental concepts and mechanisms, describes manufacturer and payer perspectives, and identifies data requirements and data collection challenges related to implementation. We also provide an interview with Roger Longman, a subject matter expert on risk-sharing arrangements, and we specifically asked him to comment on things from the standpoint of the current pandemic. Can we expect a major impact? Turn to his Q&A to find out.

On a final note, this issue of Value & Outcomes Spotlight is the last on which I will have functioned as Editor-in-Chief. I have thoroughly enjoyed my time working with a wide variety of truly outstanding people during the 12+ years I have been in this role, including the ISPOR staff, the editorial advisory board, and the various content contributors. Many thanks to all of you! Overseeing the creation and growth of this publication has been extremely gratifying and I look forward to supporting the next Editor-in-Chief in taking Value & Outcomes Spotlight to new heights.

I also look forward to connecting with friends and colleagues throughout the ISPOR community as circumstances permit us to do so safely. Let’s hope that “new normal” comes very soon.

Sincerely,

David Thompson, PhD
Editor-in-Chief,
Value & Outcomes Spotlight
ISPOR Short Courses: Learn, Apply, Advance
Christina M. Darnowski, MLS, CAE, Director, Governance and Executive Projects, ISPOR

Building skills and knowledge to strengthen and expand capabilities in health economics and outcomes research (HEOR) is at the core of ISPOR’s mission. As one of ISPOR’s strategic pillars, Education and Training endeavors to lead the development of HEOR-focused education and training programs and develop and deliver a core curriculum for HEOR professionals.

The Society’s short course program is at the center of our education programs. Since 1988, ISPOR has been delivering short courses led by world-renowned faculty. ISPOR’s short courses have since become the hallmark prologue to our annual conferences. This very successful program has grown from 8 courses with 171 participants at the 3rd International Meeting in Philadelphia, PA, USA to 37 courses delivered to over 2500 registrants in Copenhagen, Denmark in 2019. More than 50,000 students have completed short course programs at our North American, European, Asia Pacific, and Latin American conferences.

This course helped me understand HEOR and better relate it to my work. [Introduction to HEOR]

This is a “must-have” foundational skillset for HEOR researchers. [Introduction to Modeling]

Best training ever! Highly relevant to my ongoing projects. [Budget Impact Analysis]

I always send my students to the ISPOR Short Course Program. The training you get there is state-of-the-art and by experts in the field.
– Daniel C. Malone, PhD, RPh, ISPOR President (2015-2016), ISPOR Short Course Faculty

Core and Specialized HEOR Topics
Covering a wide array of topics, short courses enhance knowledge and techniques in core and specialized HEOR topics, as well as in emerging trends. They provide instruction to professionals at all levels from students to senior executives. Courses are interactive, with active student participation, case studies, group and individual exercises. Participants can apply their new knowledge to their work immediately.

Scientific topics that correspond to ISPOR’s taxonomy include: Economic Evaluation; Methodological & Statistical Research; Study Approaches; Patient-Centered Research; Health Technology Assessment; Real-World Data & Information Systems; and Health Policy & Regulatory. These topics, also referred to as tracks, correspond with the competencies for HEOR professionals defined by the HEOR Competencies Framework™ initiative led by ISPOR’s Institutional Council and Faculty Advisor Council.

ISPOR’s Short Course Committee, a group of dedicated HEOR expert members that serve as part of our Education Council, work to ensure a high-quality, balanced, and relevant course offerings. Furthermore, courses offered at our regional conferences are designed to reflect the unique training needs within the region. The curriculum reflects the ever-changing HEOR field and needs of diverse stakeholder groups. Newer and very popular offerings include: US Payers: Understanding the Healthcare System; Market Access & Value of Medical Devices; and Introduction to Machine Learning Methods. Members are encouraged to submit proposals for new courses, and ideas also come from ISPOR’s Special Interest Groups and Chief Science Officers.

Going Virtual
As global populations and economies are still contending with the COVID-19 pandemic, ISPOR’s Short Course program—like the ISPOR 2020 conference—has pivoted to provide its signature education and training courses virtually. To meet the needs of HEOR professionals and those interested in the field, courses are being offered remotely in real time during June and July 2020. Virtual short courses will also be offered in conjunction with Virtual 2020 Asia Pacific. A complement of both core and trending courses are designed to provide participants with the same relevant curriculum and expert instructors offered at in-person ISPOR conferences. These virtual courses will provide participants with the opportunity to interact with faculty and other students.

In addition to short courses, ISPOR offers a variety of live and archived webinars, offering 1-hour learning sessions covering important scientific topics. Many webinars are open to members and non-members without a fee. Visit our website to review the latest webinars and other digital programs.

Together with our world-class faculty, we are committed to bringing the highest quality HEOR education and training opportunities to an international, multistakeholder audience whether in person or virtually. Claim your seat for ISPOR virtual Short Courses (available June 17th to July 30th) to keep your skills sharp.

Learn. Apply. Advance with ISPOR Essential HEOR Education.
HEOR NEWS

1 Remdesivir Helps Coronavirus Patients—But at What Cost? (Politico)
Experts believe that how Gilead navigates financial pressures from investors and political pressures from Washington may very well determine the mass production and availability of one of the most promising coronavirus drugs on the market.
Read more.

2 ICER Sets Terms of Debate on Pricing Gilead’s COVID-19 Drug (Biopharma Dive)
Gilead’s antiviral drug remdesivir, newly shown to help speed recovery in patients hospitalized with COVID-19, would be cost-effective at a price as high as $4460, according to a new analysis from the Institute for Clinical and Economic Review (ICER).
Read more.

3 The Equitable Distribution of COVID-19 Therapeutics and Vaccines (JAMA)
An editorial from Thomas J. Bollyky, Lawrence O. Gostin, and Margaret A. Hamburg in the May 7 issue says now is the time to plan for manufacturing capacity, financing, and the distribution infrastructure necessary to produce sufficient quantities of COVID-19 therapeutics and vaccines to meet global needs in a fair, public health-driven manner.
Read more.

4 How COVID-19 Has Reshaped Healthcare Delivery So Far (Health Populi)
The Health Populi blog from IQVIA shares facts about healthcare delivery during the age of COVID-19: patients have been visiting physicians’ offices or healthcare clinics 70% to 80% less than pre–COVID-19 times; the use of acute therapies have declined while chronic therapies have been stockpiled.
Read more.

5 Utilizing Real-World Data to Inform Healthcare Decision Making During the COVID-19 Pandemic: An Interview with Daniel Prieto-Alhambra (The Evidence Base)
Daniel Prieto-Alhambra (University of Oxford; United Kingdom) discusses his involvement in the recent virtual study-a-thon hosted by the Observational Health Data Sciences and Informatics community, as well as the relevance of real-world evidence to the fight against COVID-19.
Read more.

6 Coronavirus Kills People an Average of a Decade Before Their Time, Studies Find (Wall Street Journal)
People dying of COVID-19 could have expected to live for at least another decade, according to 2 studies that help fill in the developing picture of the human cost of the coronavirus pandemic.
Read more.

7 Putting a Dollar Value on Life? Governments Already Do (The Incidental Economist)
The Incidental Economist’s Austin Frakt picks up his article from The New York Times, in which he outlines how deliberations about the trade-offs between saving lives and saving the economy have been taking place in government policy for decades.
Read more.

8 Women and Black Patients Are Poorly Represented in Clinical Trials, Analysis Finds (Pharmalot)
According to an analysis by the Tufts Center for the Study of Drug Development, researchers examined trials conducted over a recent 10-year period and found that only 37% of 775 pivotal trials (which are the late-stage studies used to win regulatory approvals) provided data on ethnicity, and only 73% of the studies broke out participation by race.
Read more.

The results of an analysis conducted by the Center for the Evaluation of Value and Risk in Health suggest that although QALY (quality-adjusted life year)- and DALY (disability-adjusted life year)-based ratios for the same intervention can differ, differences tend to be modest and do not materially affect comparisons to common cost-effectiveness thresholds.
Read more.

10 EMA Preparing Big Data Q&A Guidance (Regulatory Focus)
The European Medicines Agency (EMA) says it is preparing a question and answer guidance on the application of EU data protection rules to the secondary use of health data in medicines development, evaluation, and supervision.
Read more.
11 Growth and Capacity for Cost-Effectiveness Analysis in Africa (Health Economics Letter)

According to an analysis by Ari D. Panzer, et al., although economic evidence in Africa has grown substantially, the capacity for generating such evidence remains limited. The authors say increasing the ability of regional institutions to produce high-quality evidence and facilitate knowledge transfer among African institutions has the potential to inform prioritization decisions for designing universal healthcare coverage.

Read more.

12 Balancing Value with Affordability: Cell Immunotherapy for Cancer Treatment in the US (The Oncologist)

Surveying CAR-T centers in the United States, the authors of this paper found from respondents that the financial viability rating across centers (median: 62; interquartile range: 48-69; scale 1-100) signals that economic sustainability of institutional programs for adult lymphoma is a concern, and that these dynamics may limit access to CAR-T for Medicare beneficiaries and lead to greater outpatient use of the therapy, which may limit access for medically complex patients.

Read more.

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In keeping with the theme of this issue, we’ve tried to identify recent research publications that highlight innovative pricing models for pharmaceuticals and/or medical devices. There is a large body of editorial, commentary, and promotional publications, but sparse research, and so in the end it was not an easy task to select the papers for this round. However, there have been some recently published empirical research and conceptualized frameworks, and we have identified 5 research papers that are worth reading. We hope the research highlighted will contribute to a discussion and debate about innovation, pharmaceuticals, medical devices, and pricing.

Innovative payment models for high-cost innovative medicines: report of the expert panel on effective ways of investing in health


Summary
The premise of this report from the expert panel recognizes that the current path of growth of pharmaceutical expenditures due to new high-cost innovative medicines cannot be continued indefinitely. The report also identifies the need to search for new ways to ensure that innovation “that matters” is produced, that patients have access to innovation, and that health systems are financially sustainable. It is in this context that the report leads to the discussion of innovative payment models for new medicines that could improve the way the objectives are met.

A single payment model is unlikely to be optimal for all situations, and the report outlines some broad principles that should be observed when defining specific payment models for innovative medicines and deciding on rewarding research and development in pharmaceutical products.

Relevance
A variety of different pricing models are proposed and no single payment model emerges as dominant, but this does not preclude that clusters of models will develop over time. It is probable that different countries and systems will learn from each other’s experience, and the policy toolbox will make use of several payment models, according to the most relevant problem in each case. The authors provide a detailed report that’s worth reading more than once.

Outcomes-based reimbursement for gene therapies in practice: the experience of recently launched CAR-T cell therapies in major European countries

Summary
This research provides an overview of the reimbursement schemes used for 2 novel and innovative cancer treatments, the chimeric antigen receptor T (CAR-T) cell therapies, Kymriah® (tisagenlecleucel) and Yescarta® (axicabtagene ciloleucel) in France, Germany, Italy, Spain, and the United Kingdom (EUS) as per the final quarter of 2019. The study also identifies the challenges and derives learnings about how other advanced therapy medicinal products may be adopted in the future. Both products have successfully obtained reimbursement in their labelled indications across the EUS, at relatively uniform list prices, and the paper describes in detail each country’s outcomes-based reimbursement scenarios. But it should be noted that the prices detailed reflect the list prices and do not (necessarily) reflect the actual amount paid once rebates, discounts, or performance-based payment mechanisms have been accounted for.

Defining the concept of fair pricing for medicines
Moon S, Mariat S, Kamae I, Bak Pedersen H. BMJ, 2020;368(l4726):dx.doi.org/10.1136/bmj.l4726

Summary
In this research, Moon and colleagues consider what makes a fair price for both buyers and sellers of medicines and describe a conceptual framework for assessing whether a medicine’s price is fair to each. The authors identified 4 categories to be considered when assessing fairness for sellers, and 3 categories of demand-side factors for the buyers, and combined the factors into a framework in which a fair-pricing zone lies between a price floor and ceiling. The price floor is the lowest sustainable price at which suppliers can sell a medicine. The price ceiling is the maximum the buyer can afford. Prices above the ceiling are defined as excessive and would justify regulation. A fair price for a medicine is affordable to the buyer while covering the seller’s costs and providing a reasonable profit margin. Within a fair-pricing zone, a specific price may be higher or lower, possibly reflecting value or distribution of consumer and producer surplus.
**Relevance**

This framework does not fix a fair price for a medicine through a cost plus formula but instead, it provides a way of systematically assessing whether any given price is fair by taking costs into account. The framework argues for a concept of pricing that explicitly takes into account the needs of both sellers and buyers, and the broader public interest objectives of securing innovation, sustainable supply, and affordability. Applying the framework to decision making, however, would require access to data on research and development, manufacturing, and distribution costs, which may limit its applicability.

**The price of innovation—the role of drug pricing in financing pharmaceutical innovation: a conceptual framework**

Morenoa SG, Epstein D.  

**Summary**

The aim of the research was to describe how the pharmaceutical industry finances innovation, and how deviations from the principles of value-based pricing (either by industry or by payers) can distort access to capital markets and lead to undesirable outcomes for patients, healthcare systems, and ultimately society at large.

The authors propose a conceptual framework describing the mechanism that links investors in capital markets to pharmaceutical innovation. The framework describes, from a financial perspective, the role played by key features along the life cycle of pharmaceutical innovation and the role that drug prices play in influencing the ability of pharmaceutical firms to raise money in capital markets and hence, finance pharmaceutical innovation. The framework breaks up the mechanism leading to innovation into a loop of 4 causal associations.

**Relevance**

The framework may be able to help policymakers appreciate the life cycle of innovation from a financial perspective and inform future policy proposals in the area of drug pricing. The framework may also help policymakers anticipate the impact of their proposals and ultimately guide policies towards setting optimal drug prices as a means to maximize social welfare.

In the end, this research contributes to the much-needed debate about the role of drug prices in incentivizing innovation.

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**Reimbursement pricing for new medical devices in Japan: is the evaluation of innovation appropriate?**

Tamura M, Nakano S, Sugahara T.  

**Summary**

This research assesses whether the evaluation of innovation in medical devices in Japan is appropriate, and compares the reimbursement process and issues between several product categories to illustrate this point. Detailed discussion on the overview of Japan’s medical device reimbursement policy and the price-setting rules and methodology are outlined. The paper specifically looks at 2 major types of reimbursement rules for medical devices: the rule determining the prices for individual medical devices (STM), and the rule incorporating the price as part of the technical fee for diagnostic devices (nonSTM). The research indicates that innovation evaluation gradually declined, and the authors explain the main reasons for this.

**Relevance**

The research provides a very detailed and empirical insight into the issues and the related policy reform for medical device reimbursement in Japan. In order to understand medical device pricing and reimbursement and the limitations in Japan, this paper is a must-read.
Recent trends in opioids have changed policy discussions of drug use from that of a problem—or an epidemic—to a global crisis. An estimated 27 million people suffered in 2016 from opioid use disorders. Globally, approximately 450,000 people died as a result of drug use in 2015 and about 160,000 were directly associated with drug use disorders; 118,000 dying with a opioid use disorder.

Recognizing the urgent need to address this public health crisis and the meaningful expertise that ISPOR members can make to research effective and efficient solutions, the Editors of Value in Health are issuing an open Call for Papers on a wide array of topics that could inform policy and healthcare decision making in solving the global opioid crisis.

Topics of interest include, but are not limited to:

- Systematic reviews of evidence on the root causes of the opioid crisis
- Qualitative and quantitative evidence describing the impact to patients, families, communities, and employers when touched by the opioid crisis
- Cost-effectiveness analysis and decision modeling of interventions to address the opioid crisis
- Summary of evidence for individual- and population-level preventions of opioid misuse
- Summary of evidence for individual- and population-level treatments of opioid misuse
- Commentaries on appropriateness criteria and monitoring use of opioids
- Summary of future needs, solutions, and evidence development

Submissions received before June 30, 2020 have the best chance of being included in this themed section. Final decisions regarding ultimate acceptance rest solely with the Editors.

Authors should submit manuscripts through the journal’s web-based tracking system at https://mc.manuscriptcentral.com/valueinhealth and be sure to classify their submissions as Opioid Crisis themed section.

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Attendees to Virtual ISPOR 2020 can access these educational symposia and all other presentation recordings through June 30, 2020. To access the recordings, follow the same steps you used to join the session. Registration will remain open until June 30, 2020 for anyone interested in viewing the on-demand sessions. Visit [www.ispor.org/ISPOR2020](http://www.ispor.org/ISPOR2020) for details.
Increasing the Legitimacy of Tough Choices in Healthcare Reimbursement: Approach and Results of a Citizen Forum in The Netherlands


**Section Editors:** Soraya Azmi, MBBS, MPH, Beigene, USA; Agnes Benedict, MSc, MA, Evidera, Budapest, Hungary

Everyone is a patient at some point or another. We all experience the healthcare system in the country or region we live in, and either benefit from it or suffer from lack of it at various times in our lives. This is felt more acutely at critical times such as right now with the COVID-19 pandemic spreading across countries and continents. The pandemic has demonstrated that one feature of a “good” healthcare system is one that can handle public health emergencies while also providing preventive care and addressing myriad other situations ranging from treatment of the chronically ill, to those with cancer, babies needing NICU care, or teens needing braces. To do this, difficult decisions about what to fund are critical and ways to increase “bang for the buck” like innovative pricing models need to be considered.

In order to increase the equitability of healthcare decisions in countries where democratic decision making is valued, involvement of the lay public should be an important consideration.

Often decisions about healthcare prioritizations are left to healthcare decision makers who are part of leadership or management of a government authority or a private entity, while hopefully taking into consideration inputs of leading medical experts. Most of the time and in most countries, patients and regular citizenry are not involved in those critical decision-making processes. This has sometimes led to public dissatisfaction about coverage decisions or whether or not patients represent the public and vice versa also could be further debated. Nonetheless, it would be valuable and indeed ideal to have means for the lay public to provide input into healthcare decisions.

The study described in a paper by Bijlmakers et al was interesting to this reader for this reason: the authors evaluated a method of obtaining insight into obtaining Dutch citizens’ preferences and to identify proposed criteria by citizens for decisions about benefit packages of basic health insurance. The authors selected 24 citizens to participate in a Citizen Forum over 3 weekends in the fall of 2017. The process of selecting participants was based on a pool of people who had previously agreed to participate in surveys or market polls that were conducted by a research and consultancy agency that specialized in values, motives, lifestyle, and behavior. Three participants were selected for 1 of 8 mentality groups representing different attitudes towards life such as value orientation (traditional, modern, postmodern) and status seeking (low, middle, high). For this work, participants were given a flat fee, accommodations (2 nights over 3 weekends), and free meals. Participants signed informed consents and none dropped out.

During the 3 weekends, participants had discussions in small groups and plenaries guided by 2 moderators. During this time, they worked through 8 hypothetical and preselected case studies that they used to compare and prioritize for inclusion into a hypothetical basic health insurance package. Participants were informed that not all treatments could or would be reimbursed and were given written brochures as well as a chance to interact with experts to gain a deeper understanding of the cases they were given. It was understood that the 24 participants did not necessarily have the medical background needed in order to process the contents of the studies. The types of conditions being evaluated were highly varied, including orthodontic braces for teens, Alzheimer’s disease, heartburn, attention-deficit hyperactivity disorder among children, atypical hemolytic uremic syndrome, total body scan, obesity, and hip prostheses for the elderly. Participants were made to select what services they would be willing to include in a basic health insurance package and for what reasons.

On the first weekend, participants were given general information and background on the Dutch healthcare system; on the second weekend, they received more detailed brochures and the case studies; on the third weekend, they worked in small groups to prioritize the 8 case studies. In order to gain insight between assignments of rankings, participants were made to agree or disagree on trade-off criteria. Results obtained from participants rankings were later analyzed based on the agreement of participants regarding a certain statement and divided into categories based on specified percentage of agreement. Categories were “no agreement,” “some agreement,” “much agreement,” and “near full consensus.” Based on these, the authors were able to derive 16 Citizen Forum-based criteria to be used when making healthcare decisions. Among them were medical necessity, effectiveness, availability...
of alternative treatment, prevention, whether current benefits are being taken away, feasibility, cost, affordability, appropriate use, and alternative funding.

Given the current public health emergency in many countries, healthcare funding is even more strained. An infectious disease is causing havoc in many developed countries that have for the most part of recent decades placed focus on chronic diseases. Infection as a leading cause of death previously had been a thing of the past. In less developed countries where infection continues to have a foothold, the pandemic creates more duress. Despite the multiple aspects of novelty of our present challenges, a means to include public stakeholders and patients becomes more important and should not be left on the wayside. Perhaps now the need for such inclusion is more important than ever.

References
NEXT STEPS IN INNOVATIVE PRICING MODELS:
SHARED RISKS, SHARED BENEFITS

BY MICHELE CLEARY
Mitigating uncertainty

Schroeter outlined how conditional approvals mean drugs lack “the perfect kind of dataset” that would allow a payer to determine the value and then set the price. Instead, these data limitations lead to uncertainty. “Getting hold of these data in a consistent and quality fashion is still a challenge.”

He continued, “We need to be able to track drug utilization and outcomes...to track how much of the drug was used, by how many patients, over which period of time, in which quantity, for which indication, with which outcome. But this is often a long and arduous goal.”

Challenge to find ideal endpoints

Sachin Jain, former CEO at CareMore and adjunct professor at Stanford University, Stanford, California, USA, agreed with Schroeter that pricing models are challenged by the choice of appropriate endpoints in pricing models. In other words, what makes clinical sense may not be meaningful or acceptable to all stakeholders.

Jain noted how ideal endpoints vary by disease, stating, "I think there's going to be some diseases where this type of pricing is easier and others where it's going to be harder.” He continued, “If you look at an area like cystic fibrosis [with] medicines that people need to take in perpetuity, you could think about models that are focused on certain types of outcomes. These are diseases with a clear cause and clear effect that can be measured easily.”

Endpoints may be more complicated with chronic conditions. The choice of endpoints is further complicated as new drugs are introduced with new modalities, providing longer-term outcomes. In oncology, for example, models traditionally used overall survival as the primary endpoint. Jain said that pricing models for oncology drugs are now using more surrogate endpoints, such as progression-free survival. These surrogate endpoints often lead to conflict. “The FDA is more open to the use of surrogate endpoints for drug approvals,” Jain said. “But payers don't want to pay for progression-free survival. They want to pay for overall survival.”

This lack of survival data and the inherent uncertainty that comes with that, Jain stated, creates demand for innovative pricing models. “Not having that data at hand, researchers are left with more surrogate endpoints, which from the payer perspective, puts the uncertainty back into the manufacturers’ court and off the payers’.”

Payer perspectives

Faced with uncertainty surrounding treatment outcomes, many payers are turning to innovative pricing models. Bethanie Stein, Vice President of Strategic Contracting, Purchasing, and Analytics at Humana in Pittsburgh, Pennsylvania, USA, shared her insights into how Humana has been using these models. One of the first payers in the United States to create a value-based contracting strategy, Humana has since completed over 50 of these agreements since 2012.

Stein noted that Humana typically utilizes value-based contracting in disease states where there is a lot of specialty drug use, such as oncology. “We feel that those drugs are typically fast-tracked by the FDA or offered some sort of breakthrough status, and typically approved on phase II clinical trials [oftentimes] without the rigor of standards that we see with other drug classes, like diabetes, for example.” She
From her perspective, surrogate endpoints can be problematic. "I think that a lot of manufacturers tailor the value-based contracts to their FDA label, which is unfeasible and really hard to manage," Stein reflected. She added that Humana wants to move away from surrogate markers, such as A1C or adherence, and really focus on answering value-based questions.

Humana uses its own claims data to capture some of these unknowns surrounding safety, efficacy, and total cost of care. For instance, when uncertainty surrounds product tolerability, Humana may examine discontinuation patterns. Stein provided an example of a manufacturer that argues that patients should be able to tolerate the drug for 3 months. She noted that if patients discontinue before that 3-month marker, clinical benefits are impeded by tolerability or safety issues. In this case, Humana views this event as a failed outcome and the drug manufacturer would assume the risk for that treatment.

Pricing models for cancer drugs often include progression-free survival, a common efficacy marker. She recounted how a manufacturer may tout a product’s superior ability to achieve progression-free survival at 8 months. However, if Humana’s data found that a member died or had added or changed their drug therapy, this would be viewed as a failing. In this case, she stated, the manufacturer would “go at risk.”

And finally, the manufacturer could “go at risk” for the total cost of care, where total costs of care with a new drug would be compared to the cost associated with standards of care. Stein stated, “If the total cost of care is less than the standard of care, [the manufacturers] would not assume any risk. If it was more, then they would assume more risk.”

Stein recommended that manufacturers keep it simple around safety, efficacy, and total-cost-of-care endpoints. But primarily, she encourages dialog between the payers and the manufacturers. She said, “The message that I have been sharing publicly is to say, ‘Come to us with your gene therapies, high-cost drugs, or specialty orphan oncology [products] and let’s have a conversation around what a meaningful value-based contract looks like.’”

Further data limitations
Jain emphasized that effective utilization of these models requires better outcomes data. “I think we need new ways of thinking about data and the role of health services research and outcomes research data in the development of medicines.” He cited firms, such as Vertex Pharmaceuticals, that use new methods like artificial intelligence and machine learning to extract information about diseases and treatments. These digital tools and technologies provide a new look at real-world outcomes data and real-world functional outcomes. “We’re talking about creating a new ecosystem that is going to drive and create a lot of value for the industry and for patients.”

But Schroeter cautions, “For real-world data to answer a scientific question, the data set needs to be representative of the disease so that you can make statistically sound decisions for commercial agreements (eg, geography).” In addition, he emphasized the need to incorporate stakeholder perspectives, stressing that moving to an innovative pricing model only makes sense if you can address the different stakeholder needs through that model. “If it is just a model to address one stakeholder need and for one stakeholder to benefit from it, then it will be a failure. You might succeed with one drug, but you won’t be able to repeat it with your next drug in the pipeline. I think that’s a huge miss.”

The need for regulatory changes
Both Stein and Jain felt these innovative pricing models could be improved through regulatory changes. Stein stated, “I would love for more plans and payers to come up with similar strategies and push manufacturers the way that we are pushing them versus allowing manufacturers to dictate a value-based contracting strategy.” But she notes that regulatory barriers would need to be removed. “It would allow both sides to take on more risk. It would improve access to those really high-cost gene therapies if we were able to share in that risk.”

Jain echoed this call for regulatory reform, arguing the need to simplify both how we measure value and how we pay for value. He stated, “I think the challenge is that this is really a regulatory environment where a lot of pricing is tied to average wholesale price across the marketplace.” Jain continued, “If you have an outcomes-based pricing model [where], for whatever reason, the outcomes are poor and there’s zero payment, the model actually takes the average wholesale price of the drug. That influences how government payers and others actually pay for those medicines.”

Challenges along the value chain
While Jain believes that introducing value-based pricing is very straightforward, he argues that paying for value is complicated by the large number of participants within a value chain. “I would say the implementation is stymied by the great...
complexity of what it takes to actually get drugs into the hands of patients."

With so many participants along the value chain, administering value-based programs where the simplest level would involve rewarding a drug manufacturer developer for a particular outcome becomes untenable. "It's oftentimes hard to attribute where the true outcomes improvement comes from," said Jain. "As a result, attempts to capture value sometimes overreach because while there are few clear cases where the value is produced entirely by the medicine, the value could have been produced by other parts of everything that goes into delivering care for the patient, [and] the clinical model in which the care is delivered."

"The challenge is that sometimes the right thing involves short-term pain to create long-term gain."

Schroeter voiced his concerns surrounding who should pay for products that generate benefits over time, especially if they fail to generate cost offsets. In these cases, he asks how we can spread the costs over the period of benefits, especially if the product is only administered 1 or 2 times to the patient. This is especially problematic in the United States where patients can readily switch payers. "Why would I as a payer pay for something upfront when the next payer then benefits from a healthy patient and I carry all the burden?"

Pricing demonstration projects
Jain proposes an entirely new framework for measuring the effectiveness of medicines and for paying for the value created, but notes the problem is identifying which party should own all of the risk. "The question is whether there is going to be some kind of company that owns all the risk. That's technically what health plans should be doing, but they're not really organized to do that because they don't often own all the elements in the care delivery and all these other pieces."

He argues that to make these models work, we need further evolution in the structure and design and organization of healthcare delivery in the United States. "I think we need to develop demonstration projects for pricing models—some bold demonstrations of value-based/outcomes-based pricing in practice," Jain said. "You could imagine a whole new category of companies that could take risks for specific diseases and build a set of solutions that include medicines, and lifestyle interventions, and ultimately try to optimize outcomes for particular types of patients. And you see pieces of these types of companies all across the marketplace."

Jain proposed that his former organization, the Center for Medicare and Medicaid Innovation (CMMI), be a participant in such a project. "I think the federal government, being the largest payer in healthcare, has a role to play. There's an increasing level of engagement between CMMI and pharmaceutical manufacturers. I think there's some interesting work potentially going on in insulin and diabetes outcomes. I think once the federal government and Medicare/Medicaid start playing in the space, I think it becomes easier for everyone else to play in this space."

Affordability remains the challenge
While these models may help mitigate uncertainty and help payers manage their budgets, affordability remains a primary concern, especially under current budget constraints. In this regard, Schroeter argued, "It's not a clinical problem. It is really a problem of how to deal with it economically."

"Affordability doesn't necessarily mean 'cheap,' but it needs to generate significant cost offsets to help reduce overall healthcare spend," said Schroeter. "I think you get into increasing the conundrum by trying to justify from a health economics perspective that it's something [that] makes sense." Jain understood how payers might rationalize the high cost of a drug or therapy this way: "Yes, it's expensive, but it helps me save costs overall by reducing hospitalization and by moving a chronic disease into a curable state." He continued, "Thinking through these kinds of paradigms and generating significant cost offsets, even in a budget-constrained environment, can make drugs affordable despite the fact that they are high priced."

Turning crisis into opportunity
As health systems globally face even further budgetary constraints under the current COVID-19 crisis, Jain remains optimistic. He sees opportunity for change that will improve pricing processes. "Crisis moments like COVID-19 give us an opportunity to really look at how things are organized now... evolving to a clearer view of what the country needs."

"I think as we formulate a view of the future, we have to be flexible in our thinking, cognizant of the current crisis, but not overly reactive to it either. The challenge is that sometimes the right thing involves short-term pain to create long-term gain. What I believe we need more of is courage."

About the Author
Michele Cleary is a HEOR researcher and scientific writer with more than 15 years of experience in the healthcare field.
By the Numbers: Innovative Pricing Models

Section Editor: The ISPOR Student Network

Models to Make Drug Pricing More Sustainable

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<th>MODEL</th>
<th>DESCRIPTION</th>
<th>EXAMPLE</th>
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<td>Suitable when large quantities of drug are required</td>
<td>Flu shots</td>
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<tr>
<td>02 Indication-specific pricing</td>
<td>Suitable for drugs approved for more than one indication/disease type</td>
<td>Monoclonal antibodies approved for multiple indications</td>
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<tr>
<td>03 Subscription model</td>
<td>Suitable when unlimited access to drug is required over a set time period for a fixed payment</td>
<td>Curative therapies such as those for hepatitis C</td>
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<tr>
<td>04 Health outcomes-based contracts</td>
<td>Suitable for expensive drugs where reimbursement can be tied to clinical effectiveness</td>
<td>Gene therapies</td>
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<tr>
<td>05 Mortgage model</td>
<td>Suitable for drugs with limited competition</td>
<td>Orphan drugs for rare diseases</td>
</tr>
</tbody>
</table>

Financial Models Used by Pharma

![Bar chart showing the percentage of pharmaceutical executives using different financial models by country.](chart1)

*Numbers represent % of total executives interviewed for each country.

Responses from pharmaceutical executives (100 respondents) across the world regarding financial models used by their organization, besides value-based contracts (February 2019)

Value Drivers in Outcomes-Based Contracts

![Bar chart showing the value drivers for payers and manufacturers.](chart2)

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Acknowledgement: We would like to thank Zeba Khan, RPh, PhD for her review and helpful comments.
Confusion abounds as to what virtual research is, what it should be called, and whether there are distinct types of it in the real world.

Introduction
Virtual approaches to clinical research leverage digital technologies to relieve study sites of many, if not all, responsibilities of the research process—from identifying potential study subjects to screening them for eligibility to obtaining their consent for enrollment to entering their study data.

Such approaches have the potential to unleash the power of the patient by bringing the research process to patients versus requiring patients to bring themselves to the research process. Doing so makes sense, as statistics suggest that less than 5% of the population ever participate in clinical research (even though the vast majority report being willing to do so), and study location ranks second only to receiving placebo among the most disliked aspects of clinical trial participation.1 There are also cost savings at stake, as reductions in site involvement and investigator burden associated with virtual clinical trials.2 While 17% said they simply “did not know how to start,” 23% cited “perceived regulatory risk” and 38% pointed to “risk associated with novel technology” as the problem.

These concerns, along with the naturally sympatico relationship between digital technologies and real-world measures, have led to a disproportionate growth in the use of virtual approaches in the real-world setting as opposed to randomized controlled trials. Nonetheless, it is still the case that confusion abounds as to what virtual research is, what it should be called, and whether there are distinct types of it in the real world. The objective of this paper is to bring clarity to these issues.

Virtual Research: What Are We Talking About?
In 2018, the National Academies of Sciences, Engineering and Medicine held a multistakeholder workshop to identify challenges and opportunities for the conduct of virtual clinical trials.3 The workshop proceedings contain a tidy and unambiguous definition of what virtual trials are but seem to lack consensus on exactly what to call them. Virtual trials are defined as “…clinical trials in which all or part of the study incorporates digital health technologies and enables remote participation outside of the traditional brick-and-mortar study sites.” Candidate umbrella terms for this kind of research were more heterogeneous, with “virtual” retained in the workshop title but “decentralized,” “remote,” “site agnostic,” “direct-to-participant,” “location flexible,” “mobile,” “flexible,” and even “modern” and “21st century” suggested as possibilities by workshop participants.

The workshop proceeds with the fact that biopharmaceutical companies are actively seeking opportunities for “going virtual” in their clinical development programs.
Figure 1. Traditional versus Virtual Research Approaches Contrasted.

<table>
<thead>
<tr>
<th>Traditional Approach</th>
<th>Virtual Approach</th>
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<tbody>
<tr>
<td>Directly via observation/measurement</td>
<td>Indirectly via connected devices</td>
</tr>
<tr>
<td>Brick &amp; mortar study sites</td>
<td>Where?，Wherever patients roam or dwell</td>
</tr>
<tr>
<td>Patients &amp; study personnel together</td>
<td>Who?，Patients alone (generally)</td>
</tr>
<tr>
<td>Research-specific data only</td>
<td>What?，Research-specific and/or ‘personal’ data</td>
</tr>
<tr>
<td>Prespecified intervals per protocol</td>
<td>When?，Prespecified intervals and/or continuously</td>
</tr>
<tr>
<td>For research purposes only</td>
<td>Why?，Sometimes for research, sometimes not</td>
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</table>

participation on the part of the US Food & Drug Administration, has released recommendations for what they refer to as “decentralized clinical trials,” suggesting a preference for that terminology. At this point, the terms “virtual” and “decentralized” are used more or less interchangeably, but as virtual approaches increasingly take root in the real-world setting, it is important to replace the term “trials” with “research” in recognition that the vast majority of real-world research is not trial-based. Hence, our use of the term ‘virtual research’ throughout this paper.

To further establish exactly what we mean by virtual research, it is instructive to contrast it to traditional approaches in terms of a variety of questions related to data capture. This is summarized in Figure 1.

The how and where of data collection are fairly straightforward—in traditional research approaches, data are collected via direct assessment of study subjects at study sites, while virtual approaches eschew direct observation in favor of remote data capture via connected devices wherever patients happen to be. The who of data collection involves patients and study personnel together in traditional approaches, while patients are generally all alone in virtual studies (although there is some human interaction when telemedicine teams are utilized).

Finally, in traditional research the what, when, and why of data collection are all strictly guided by the study protocol, which governs that only research-specific data are to be captured, almost always at prespecified intervals. In contrast, things are more open in virtual approaches, as digital technologies capture research-specific data but also “personal” data along the way, and this can be done according to prespecified intervals or continuously. Indeed, in some instances, none of the virtually captured data were initially intended for research purposes, and this is important as we start thinking of classifying the different types of virtual research in the real-world setting.

A Classification Scheme for Virtual Research in the Real-World Setting
Real-world data sources can be distinguished along various dimensions, but for our purposes it is useful to focus on 2 in particular: one characterizing how the data are collected (active versus passive) and the other distinguishing the temporal aspect of data analysis (retrospective versus prospective).

Active data collection involves use of case-report forms, instruments or other means of data capture, where data are specifically collected for research purposes and patients are actively involved in sharing their data. In contrast, passive data collection refers to accrual of data in information technology systems as a by-product of real-world care processes or other patient activities. In this case, the data are not initially collected for research purposes but can subsequently be manipulated for use in research, and patients are not always mindful of the act of sharing their data.

The prospective versus retrospective distinction is straightforward, with prospective research involving the analysis of data collected from the present into the future and retrospective research involving analysis of data collected in the past.

Figure 2. Two-by-Two Typology of Real-World Data Sources, Highlighting Digital Technologies.

When we combine these distinctions in a simple two-by-two typology (Figure 2), we can first see how the familiar real-world data sources (in black font) are sorted: pragmatic clinical trials and noninterventional studies such as registries in the upper-left quadrant; patient charts and computerized databases in the lower right; and population registries in the upper right. We also see that digital technologies (in red) appear in all 4 quadrants as a source of real-world data.

This enables us to start distinguishing different kinds of virtual research:

**Actively Collected/Prospective Research.** These include studies where connected devices are used to measure “novel endpoints” in both interventional and non-interventional prospective studies. In all other respects, these studies are similar to traditional prospective studies in that they require ethics approval, informed consent, a protocol to govern data collection, the whole nine yards.

An interesting example of this kind of real-world research is the “Cloudy with a Chance of Pain” study, which piloted an app designed to assess associations between weather and joint pain in patients with rheumatoid arthritis. Participants entered self-reported pain, fatigue, physical activity and other data into the app on a daily basis for 60 days. Global positioning systems (GPS) embedded in their smartphones enable linkage to local weather conditions, thereby allowing weather data to be pulled into the study database and matched by time and location to patients’ symptom data. Analyses of these data assessed associations between weather data and various measures of chronic pain, and found that higher relative humidity and wind speed and lower atmospheric pressure were associated with increased pain severity in people with long-term pain conditions.
**Actively Collected/Retrospective Research.** These studies require de novo creation and curation of a database, are guided by a protocol, and require identification and recruitment of a study cohort and arrangements for data collection via digital technologies. Ethics approval and informed consent are required, as is the case with traditional population registries.

An interesting example of this type of real-world research is the “All of Us” population-based research program that is seeking to enroll a diverse group of at least 1 million people in the United States to accelerate biomedical research and improve health. Elements of the protocol include health questionnaires, electronic health records, physical measures, and the collection and analysis of biospecimens. Although not an example of fully virtual research, study participants have the option to contribute data from their wearables and sensors. The program launched in May 2018; one year later, the program had met more than one-fifth of its recruitment goal.

**Passively Collected/Retrospective Research.** In this type of research, data flow automatically to the device/app developer without a protocol and with no active patient involvement. Consent for data sharing is handled via opt-in at the time of device/app registration. No formal ethics approval is required, nor is any advance work on the part of the researcher. The most common type of real-world data in this category derive from wearables, which have the capacity to continuously transmit data back to the study database without active engagement on the part of the wearer.

An example of this research is the Fitbit Sleep Study, which tapped Fitbit’s longitudinal sleep dataset—built from millions of nights of data obtained via its Sleep Stages app—to determine how age, gender, and other factors affect sleep quality. The Sleep Stages app uses motion detection and heart rate variability to estimate the amount of time users spend awake and in light, deep, and REM sleep each night. Data flow automatically to the database on a nightly basis, thereby leading to an ever-expanding dataset accessible for use by researchers, all of which occurs without any overt effort on the part of Fitbit users.

The digital revolution in health is invading the clinical research realm, and nowhere is this invasion more pronounced than in the real-world setting. The COVID-19 pandemic has acted to accelerate these developments on all fronts.

Another, more timely example that has gained prominence during the COVID-19 pandemic derives from data collected by smart thermometers. One manufacturer of these thermometers, Kinsa, has created a website containing a heat map of elevated temperature readings derived from users of their device, which utilizes GPS technology to aggregate average temperature readings across the United States. Historically, elevated temperature readings have been a leading indicator of flu outbreaks and now do the same for COVID-19.

**Passively Collected/Prospective Research.** In this type of study, data flow automatically to the device/app developer or to the study database (if separate), with no active patient involvement. In this instance, however, a protocol is required for identification and recruitment of the study cohort, and arrangements for data collection via the app(s) and device(s) involved. Ethics approval and informed consent are required.

The Apple Heart Study, a prospective observational cohort study, that has enrolled more than 400,000 participants to test the ability of a smartwatch algorithm to identify pulse irregularity and variability that might reflect previously undiagnosed atrial fibrillation. Patient screening, consent, and data collection all happen electronically via an accompanying smartphone app, and the only thing that participants are required to do in the study is wear their Apple watches. Additional patient engagement and data collection are undertaken only for those participants in whom irregular heart rhythms are observed.

This simple classification scheme demonstrates how digital technologies fit in with other real-world data sources and facilitate greater understanding of different kinds of virtual research in the real-world setting. Some virtual studies will be more like traditional prospective observational research—and therefore take on the characteristics of registries, for example—while in other instances, real-world data collected by means of wearables and other connected devices will be tapped into for retrospective analyses, in much the same way claims databases have been for the past few decades. Recognizing these differences is essential to fully appreciating the nuances of virtual research in the real-world setting.

**Challenges in Virtual Research Execution**

In addition to presenting challenges to real-world research design, virtual approaches involve a host of challenges in study execution.

Not surprisingly, these challenges derive from the elimination of study sites and the critical role that site-based staff play in the research process. Here are 3 broad challenges that virtual approaches impose on study execution:

1. **Patient recruitment**: How to identify potential study subjects without investigators to refer their patients and without site-based personnel acting as intermediaries and facilitators.

2. **Ascertainment of eligibility**: If patients complete screening forms remotely, by themselves, how to ensure that they actually meet key eligibility criteria for study participation without corroboration from study sites.

3. **Assurance of patient reliability**: How to get patients enrolled, stay engaged, and complete data collection without site support.

As these issues make clear, virtual research puts a far greater onus on patients to drive the success of the study—so we can see that patient centricity carries with it increased patient responsibility in the research process.
Fortunately, the same technologies that make virtual research possible provide solutions to the implementation challenges to which virtual approaches give rise. Patient identification can be facilitated by geo-targeted digital recruitment, such as pop-up ads on social media outlets and internet search engines. Patient eligibility can be ascertained by including electronic medical records access in the consenting process, thereby permitting the study team to contact the patient’s healthcare provider to confirm diagnosis, medical history, medication use, and the like. And smartphone apps can be programmed with reminders and gamification elements to ensure that patients continue to transmit data and stay engaged throughout the study duration.

The Road Ahead

The digital revolution in health is invading the clinical research realm, and nowhere is this invasion more pronounced than in the real-world setting. The COVID-19 pandemic has acted to accelerate these developments on all fronts. Manufacturers remain cautious about deploying virtual approaches in their phase II-III clinical trials and have come to view the real-world setting as a lower-risk testing ground for innovation. Understanding how real-world data derived from connected devices compare to the sources we are already well familiar with is critical to sound study design—just as we readily discern a database analysis from a registry study, we should similarly be able to distinguish between different types of virtual research. For now, during this nascent phase of virtual research, the simple two-by-two typology described in this paper may prove useful, but look for it to give way to more complex classification schemes as further examples of virtual approaches proliferate in the real-world setting.

References

New outcomes can capture specific aspects of disease and treatment benefits not included in traditional endpoints. These aspects can reflect change in treatment paradigms, disease course, and treatment pathways. New outcomes also need to be tailored to the patient experience, and assessment frameworks at NICE take them into consideration.

New outcomes, such as the ones derived from wearables or patient experience, are designed to capture actual value to patients and reflect changes in treatment paradigms, disease course, or treatment pathways. Four experts, who are also the authors of this article, held a panel at the ISPOR New Orleans conference in 2019 on the introduction and impact of new outcomes on coverage decisions.

What Do New Outcomes Bring? Similarities and Differences With Regulatory Decisions

With the emergence of innovative, potentially curative, and expensive treatments in the past decade, coverage and reimbursement decisions have become increasingly complex and accordingly scrutinized.

Helene Karcher introduced the topic and compared the use of new outcomes in the regulatory and reimbursement settings. New outcomes have been presented to payers and health technology assessment (HTA) bodies to make the case for coverage or reimbursement decisions. How can these new outcomes improve decision making? How much do they actually impact decisions? And what is the best way to introduce them to payers?

Most traditional clinical trial endpoints and outcomes that measure the effect of a treatment or intervention come from daily medical practice. That is, they were designed to assess the health of a particular patient by their physician or nurse. They are a metric for “hard” clinical observations, and new outcomes can capture specific aspects of disease and treatment benefits not included in traditional endpoints. These specific aspects can reflect change in treatment paradigms, disease course, and treatment pathways. This is particularly relevant in rapidly changing treatment landscapes, such as many cancers (e.g., renal cell carcinoma, prostate cancer, etc) or chronic diseases that are becoming better understood and described (e.g., non-alcoholic steatohepatitis or neovascular age-related macular degeneration).

Second, these new outcomes can capture value to patients and caregivers, which are not always directly measured as part of routine clinical care nor considered as a clinical endpoint by regulators and payers. The patient experience is particularly of interest when products are potentially impacting on quality of life and/or the price is at parity. Moreover, payers as well as the public need to understand the added benefits of new treatments compared with potentially cheaper generic treatments. Patient experience is herein defined as benefits in outcomes that are not covered in biological realities, but rather defined by subjective experience ratings (such as treatment convenience, satisfaction, and other indirect improvements).

New endpoints historically have faced challenges at the regulatory approval stage and are now facing similar ones at the coverage decision stages. Namely, the fact that there is no precedent makes it difficult to compare new products with existing therapeutic agents. Whenever clinical trials with comparator agents have captured the new endpoints, indirect treatment comparison is only possible if a de novo head-to-head trial that includes the new endpoint is conducted comparing the new product with the existing one. For this very reason, new endpoints have been introduced and presented for regulatory decisions mainly as secondary or exploratory endpoints, with pivotal trials keeping traditional endpoints as primary.

“...new patient-derived outcomes are starting to weigh more heavily into coverage decisions for new treatments.”
The increased attention to patient experience in their treatment journey, be it through an increase in quantitative studies or surveys, or using new clinical outcome assessments, has also triggered questions at the reimbursement and coverage decision stages about the value of treatments for patients, beyond clinical efficacy. While regulatory decisions have traditionally focused on clinical efficacy, coverage decisions are focused on value to patients, which require different patient-derived endpoints. Many health technology assessment agencies use generic preference-based endpoints, such as EQ-5D, to measure quality of life. These endpoints are critical for understanding the health benefits for a patient and the population at large—as normative population values have been obtained that may be used to evaluate population health gain. Nevertheless, these quality of life measures may lack sensitivity in some disease areas (eg, gout and ophthalmology).

Examples of Novel Patient-Centered Endpoints

Disease-specific assessments are not available in all diseases and/or may not adequately capture the patient experience undergoing new treatment. This can mean that some assessments do not capture data when the patient experiences an improvement or when patients do not answer questions completely. Unresponsiveness and/or missing data in patient-reported outcomes may lead to innovative treatments not being covered. Patients and clinical specialists often then agree to develop new methodological standards that better measure disease progression, capture patient experience, or characterize therapeutic benefit. An outcome measure that is tailored to the patient experience is often more sensitive to change under treatment (ie, is able to demonstrate treatment benefit). The results of a new treatment instrument also allow clinicians to articulate more clearly to patients and clinicians what the new treatment can offer.

In the panel discussion, Katja Rudell spoke from a perspective as a methodologist. She helped to develop 3 new clinical outcome assessments that measured disease progression better than existing measures: (1) the use of wearable actigraphy combined with symptom reduction in chronic obstructive pulmonary disease [the PROACTIVE tools]; (2) a symptom diary that captures better issues of swelling and impact of arthritis in gout; and (3) an asthma control diary that captures not only reduction in symptoms and hospitalization, but also well-being, a concept that is broader than health costs (Figure 1). All were clinical outcomes assessments derived from patients’ understanding of the disease, which expanded into other areas. The discussion within the panel was centered around whether pharmaceutical companies are encouraged to consider and utilize new endpoints when standard endpoints are not fully reflective of disease progression and/or treatment impact.

An Industry Perspective: Using Patient Experiences to Demonstrate the Need of a New Endpoint

Stephane Regnier presented a manufacturer’s perspective. Diseases are often multifaceted and current clinical endpoints might not capture all dimensions. Hence, additional endpoints can be useful. However, payers want consistency between decisions, and new endpoints can become challenging to assess for reimbursement decisions. In addition, a skeptical payer may wonder why the manufacturer decided to include a new endpoint in its

![Figure 1. Examples of 3 new endpoints capturing patient experiences.](image-url)

3 new endpoints – Asthma Control, Gout and COPD

<table>
<thead>
<tr>
<th>Asthma Control Means</th>
<th>Gout Feet Assessments</th>
<th>COPD - PROACTIVE</th>
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<tr>
<td>Symptom control</td>
<td>RA tools are missing</td>
<td>Activity limitations are one of</td>
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<td>Remove activity restrictions</td>
<td>important issue for Gout</td>
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<td>Remove emotional turmoil</td>
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<td>New tools needed</td>
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<td>PROactive diaries</td>
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COPD indicates chronic obstructive pulmonary disease; PRO, patient-reported outcome, RA, rheumatoid arthritis.

Fig 2. Importance and difficulty to perform different activities in patients with nAMD (n=26).

* Percent of patients scoring a bit or very difficult, or stopped due to eyesight.

** Percent of patients scoring very or extremely important.
Neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME) are good candidates for new endpoints. With the advent of antivascular endothelial growth factor agents,1,2 and intravitreal injection of steroids3,4 more than a decade ago, treatment outcomes for patients have improved greatly, and vision and the quality of life of patients can be preserved in many cases.5 However, as patients today present earlier with better baseline vision, are treated earlier, and tend to maintain but not to gain better baseline vision, are treated earlier, as patients today present earlier with better baseline vision, are treated earlier, and tend to maintain but not to gain vision; the best corrected visual acuity, a functional endpoint commonly used in regulatory trials in retinal diseases,7 may no longer capture the impact of treatment in today’s patients with nAMD and DME.

Multinational, individual, structured interviews were conducted with consenting patients with nAMD or DME in Canada, France, the United Kingdom, and the United States to identify activities that patients find both important and difficult to engage in. In order to demonstrate that some vision-dependent activities are impaired despite good best-corrected visual acuity, interviewed patients had moderately reduced best-corrected visual acuity <1 year (defined as ≥64 letters on an Early Treatment Diabetic Retinopathy Study chart). A total of 46 patients were interviewed; 26 with nAMD and 20 with DME. Interviewed patients had a current average best-corrected visual acuity of 74 letters. We found that, among patients with no or only moderate reductions in their eyesight measured on standard scales, a majority still experienced difficulties with activities in their daily lives (Figure 2). This indicates a need to include additional measurements of reduced vision when assessing the impact of disease or its treatment on patients’ experiences. Functional tests such as measures of contrast sensitivity, adaptation to darkness, and reading speed may be more useful and correlate better with patients’ ability to perform important activities of daily living.

**HTA Perspective on New Outcomes**

Pall Jonsson presented the view on new outcomes from the health technology assessment perspective. He explained 3 different frameworks that the National Institute for Health and Care Excellence (NICE) uses for development of guidance.

The first framework is used for Technology Appraisals, which chiefly covers the assessments of drugs. The methods for Technology Appraisals set out the reference case which, among other things, is intended to guide the selection of outcomes that inform the appraisal. The perspective of outcomes is to consider all direct health effects, whether for patients, or when relevant, for caregivers. NICE prefers health effects to be measured by the EQ-5D instrument reported directly from patients and converted into quality adjusted life years. However, in all appraisals, a consideration is given to how relevant to patients these standard measures are in the context of the disease or the condition being appraised. Jonsson referenced a number of appraisals where the NICE appraisal committee has concluded that the full benefits of treatment have not been fully captured by the standard EQ-5D instrument, therefore highlighting the importance of new patient-derived outcomes that could help in these cases.

The second framework is used in the production of clinical, public health, and social care guidelines.8 The nature of guidelines, usually covering much broader treatment pathways than technology appraisals, means that the scope of outcomes that are used in guideline development is broader. Quality of life using EQ-5D is always in scope, but outcomes that are specific to the condition and are deemed important to patients and caregivers are also in scope, with a special focus on core outcome sets that are specific to the disease or the condition under consideration.

The third and the newest framework is the Evidence Standards for Digital Health Technologies. This is an assessment framework that applies to digital tools in healthcare, including apps and digital clinical decision aids. While different standards apply, based on the potential function of the technology and the risk to the users, the outcome measures reported should reflect best practice for reporting improvements in the specific condition, using validated outcome measures such as those in the COMET10 core outcome set.

Jonsson concluded that all these assessment frameworks at NICE are open to the use of new patient-derived outcomes and endpoints. However, in all cases, it is imperative that the relevance of the outcome to patients is demonstrated and the validity and

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**Figure 3. A survey of European healthcare decision makers on the acceptability of patient-reported data for effectiveness research and healthcare decision making.**
quality of the instrument and data are established. As an indication of the appetite to use new patient-derived outcomes in the future, Jonsson presented a review conducted by the IMI GetReal Initiative in which European healthcare decision makers, including those representing payers and health technology assessors, were asked about their views of patient-derived data for in their decision making. As shown in Figure 3, while a small proportion (10.5%) indicated that they would not support the use of these data, the majority (68.5%) took a more favorable view. The quote of one particular decision maker is inspiring and illustrates the importance of valuing what the patient values: “We need to get people's views as to effectiveness of treatment, rather than just clinicians. If we don’t listen to them, how will we ever optimize their care?”

Summary

New medicinal products are under increased scrutiny for the value they provide from the patient perspective. This has led to new patient-derived outcomes starting to weigh more heavily into coverage decisions for new treatments. These new outcomes face similar challenges for validation as the ones new endpoints face at the regulatory stages. Examples in gout and ophthalmology indications show that new outcomes can be more sensitive to change under treatment than traditional endpoints and better capture the value of new treatment to patients.

References

Massive expansion in the availability of data combined with advances in analytic methods create tremendous opportunities for HEOR analyses. But multidisciplinary teams will be necessary to realize these opportunities.

There are a variety of analytic methods available to researchers for approaching different types of health economic evaluation problems. Most researchers have expertise in a specific analytic method such as health economic modeling or causal inference from health econometrics/epidemiology. More recently, we are seeing an increased use of constrained optimization and simulation methods. These methods are often highly complementary, but analytic opportunities are lost because deep methodological domain knowledge keeps researchers locked within their own methodological silos. For example, discrete event simulation methods are widely used in health economic modeling, and causal modeling methods are often a precursor to estimate the parameters in health economic models or building the equations in a simulation model. In this article, we consider 4 major analytic methods: (1) health economic modeling, (2) causal modeling, (3) simulation modeling, and (4) constrained optimization modeling. We propose that the complementarity of the insights produced by the different methods argues for the benefits of building interdisciplinary teams of researchers with different methodological skillsets.

Health Economic Modeling: Building the Patient Footprint

Health economic modeling is widely applied in cost-effectiveness evaluations of pharmaceutical products, devices, and other interventions by health technology assessment organizations and payers to assess the value of new treatments. Why do we need modeling? One important reason is that the data necessary to conduct cost-effectiveness analyses typically reside in different places and must be combined using a modeling framework. As indicated in Figure 1, many different inputs are needed for health economic models. These include treatment effectiveness, cost and resource use, quality of life, and adverse events. For example, health technology assessment organizations typically evaluate new technologies following marketing approval by regulatory authorities. The primary information available at the time of approval is the efficacy and safety evidence from the randomized controlled trials used for the regulatory submission. Since there is no market evidence based on experience with the product yet, the cost and patient utility data must be gathered from other sources for similar patient populations. It is also important to understand the natural history of disease for the condition being evaluated, and it is necessary to understand the quality of the data sources for each of these inputs. Due to the maturity of the health economics modeling field, there are many guidelines for building health economic models.

Figure 1. Inputs for health economic models.

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<th>TYPES:</th>
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Causal Modeling: Estimating the Impact of an Intervention
The strongest causal inferences come from randomized designs that balance interventions on both observable and unobservable confounders. Randomized designs also greatly simplify the statistical analysis of treatment effects. However, for many reasons, evidence from randomized trials often is not available. As a result, researchers attempt to draw causal inferences from secondary data sources not originally intended to support research. After a product has been on the market long enough, evidence on a product begins to accumulate in medical claims and electronic health records. We have good statistical methods for addressing many of the issues that arise in the analysis of observational data. However, in observational analyses, we need to be careful about design and statistical methods in order to arrive at reliable inferences. The methods from epidemiology—propensity score, inverse probability weights, G-estimation, and so forth—are extremely important, but the most important contribution from epidemiologists is what they’ve taught us about research design. Economists have developed a complementary set of methods that use empirical correlations in the error structures of models to correct for a wide variety of measurement and specification challenges common in real-world data analysis. These include parametric and nonparametric sample selection bias models, as well as a broad range of simultaneous equations methods.

Simulation Models: Analyzing Complex Systems
Simulation models use the results from causal models and health economic models to evaluate problems from a systems perspective. This requires thinking about the context (including the people, technology, and healthcare settings) in which these services and technologies are delivered. Healthcare delivery processes include feedback loops, as well as nonlinear and spatial relationships among entities, multiple agents or stakeholders, time dependency and dynamic transitions within the system, and the idea of emergency. “Emergency” is not used in the context of being urgent, but rather how things emerge downstream, resulting in intended and unintended consequences in the system. For example, it is very difficult to anticipate how patients will interact with the healthcare system, and how this will affect individual patient outcomes and health system performance outcomes (eg, wait times). The key idea around simulation modeling is to model the complexity of the system, and then evaluate results for various “what if” scenarios to inform planning for healthcare services delivery. Importantly, simulation enables assessment not only of intended effects but also unintended effects that may not be anticipated due to system complexity. Using simulation modeling makes it possible to explore and anticipate the impact of potential changes without actually altering the system until a strategy or policy has been identified that improves overall system performance.

Constrained Optimization: Using Math to Set Policy
A fourth methodological approach is constrained optimization. The term “optimal” is widely and loosely used in healthcare. Constrained optimization is a mathematical approach to finding the truly best solution to a problem, subject to real-world constraints. In health technology assessment analyses, for example, we can use constrained optimization to identify the most cost-effective policy decision subject to real-world constraints such as the health system budget. Constrained optimization methods are a tool for dealing with the combinatorial complexity of healthcare problems that overwhelm decision makers leading them to make suboptimal decisions. They consist of an objective function that we are trying to optimize (eg, minimize the number of cervical cancer cases), a set of decision or policy variables (eg, cervical cancer screening or vaccination for human papilloma virus), a set of parameters for each of the decision variables (these are externally determined prior to the optimization modeling), and a set of constraints (eg, budget constraint). As with each of the other methods, there are many different types of constrained optimization modeling approaches, depending upon the problem.

Matching Methods to Problems: the COVID-19 Pandemic
In this overview, we have briefly summarized 4 major types of methods: health economic modeling, causal modeling, simulation modeling, and optimization modeling. And although there are many different methods that are used in health economics and outcomes research, it’s probably fair to say that most fall within these 4 major types of methods.

The COVID-19 pandemic sweeping the globe provides a poignant example of how the 4 methods can be applied to address different components of a critical problem. The COVID-19 pandemic sweeping the globe provides a poignant example of how the 4 methods can be applied to address different components of a critical problem. The nonlinearity of disease transmission, the differential mortality among alternative population subgroups, and the differential supply of medical services across geographies all render the traditional methods used by health systems inadequate to anticipate where critical shortages in needed care may occur. This is a problem that is tailor-made for simulation models. SIR models from epidemiology are systems of differential equations that model the population susceptible, infected, or recovered (or, alternatively, removed). The parameters in the model are calibrated for local characteristics and enable “what if” simulations in response to changes in assumptions. Agent-based simulation models can extend SIR models to include agents interacting with different groups in the community such as schools, places of employment, grocery stores, or the healthcare system. Similarly, one could use discrete event simulation to estimate the demand for specific types of healthcare services that could then be evaluated given the level of local supply (eg, number of hospital beds, ventilators, nurses, and physicians) available through real-world data analyses. After the first
wave of the pandemic has passed, a tremendous amount of data will have been generated on how patients were treated. These data reflect a series of natural experiments that enable the performance of alternative treatment approaches to be assessed using causal inference methods. Similarly, the cost-effectiveness of these alternative treatment approaches can be assessed using health economic modeling. Finally, assuming that some of the existing therapies used to treat COVID-19 patients were shown to be effective, or newly developed therapies have become available, constrained optimization methods could be used to design optimal screening and treatment protocols. This has already been done successfully for the treatment of influenza. In short, it is likely that all 4 categories of models will be highly relevant for dealing with the COVID-19 pandemic and preparing us for subsequent waves of the virus.

The COVID-19 example illustrates that there are multiple factors that play into selecting an analytic approach to a problem. Rarely are the methods mutually exclusive, and they are often highly complementary. The example clearly illustrates the value of considering an expanded selection of methods that may help frame a more complete solution than might be possible by staying within a particular methodological silo. To do so, however, requires an expanded skill set. ISPOR members are generally familiar with health economic modeling and the causal modeling methods from epidemiology, econometrics, and health services research. However, the skill sets needed for simulation and optimization relate to the field of operations research that has traditionally been the bastion of engineering. (Although it is clear from their use of SIR models that mathematical epidemiologists have been working with simulation methods for many years!)

**What’s Next for HEOR Models?**

Looking ahead, machine learning is yet another method that is coming to us from engineering and computer science. We are starting to see a need for teams with training in economics, epidemiology, engineering, and computer science as we move into this new environment where we have access to much more data—much of which are unstructured (Figure 2). In addition, healthcare domain knowledge is very important to augment the technical skills of the various types of modelers. Those trained solely in machine learning methods often lack experience with observational data and knowledge of the healthcare sector. Conversely, those trained in epidemiology, health economics, and health services research generally lack skills in natural language processing and machine learning techniques that will be needed to deal with unstructured data, complex data structures, and data volume that are already with us today. The health economics and outcomes research challenges of the future will require us to move beyond our methodological silos and build multidisciplinary teams.

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**References**


Balancing the needs of patients, healthcare systems, drug manufacturers, and investors has never been trickier. The old model of banking on innovation to drive sky-high prices has long since expired. Payer pushback is leading to access restrictions that are not only affecting patients on the front lines but also negatively impacting companies’ bottom line. Innovative drug pricing and value-based contracting models may be solutions for getting the price equation right from the outset.

This month’s interview with Roger Longman of Real Endpoints LLC, a leading reimbursement-focused analytics and advisory firm, discusses innovative and value-based contracting models currently in use and reflects on the downstream effects of innovative pricing on patients and their out-of-pocket costs. As a recognized expert in biopharmaceutical strategy and reimbursement, Roger provides keen insight into the practical challenges payers face in implementing innovative contracting models in different healthcare systems.

“The takeaway from COVID-19 should be that it is easier to prevent a case than to treat one. The same logic can be applied to cancer detection and treatment.”

OPPORTUNITY OFFERED BY A GOOD CRISIS: COVID-19 IMPACT ON INNOVATIVE PRICING MODELS

Interview With Roger Longman, Cofounder and Chairman of Real Endpoints LLC
Payers are beginning to exert more influence on pharmacy benefit oncologics, and as they do, pharmaceutical companies will likely start to explore innovative contracting in cancer as well as other categories.

**VOS:** What are the biggest challenges to implementing an innovative contracting model, and do the challenges differ depending on the type of healthcare/payer system (e.g., private payers versus single government payer)?

**Longman:** I'll need to divide the answer into the very big issues and the smaller, practical ones, as both are significant obstacles.

Starting with the very large: In my view, the most innovative recent arrangement was the one negotiated between Britain’s National Health Service (NHS) and The Medicines Company (now part of Novartis). It did something the United States couldn’t do: agree to buy a large volume of drug based on a preset price that ensured its cost-effectiveness, before the drug is approved. If the Centers for Medicare & Medicaid Services (CMS) or the Veterans Health Administration or any US or state government was allowed to do that, it could change things dramatically.

Another issue: Medicaid best price rules, and the opacity of how they might be applied, often limit the level of risk that biopharmaceutical companies are willing to take. CMS could change that rule with a stroke of the pen, and they should.

Perhaps most importantly, however, our private healthcare system by and large doesn’t incentivize payers to make decisions based on the real value of the intervention. They’re not paid to take the long view and thus don’t value benefits that won’t be realized for years (beneficiaries shift in and out of health plans too often). In addition, they buy and large won’t prioritize one kind of intervention over another based on a societal definition of value. When social benefits, even ones with long-term economic benefits, run up against short-term shareholder interests, the latter generally win.

This is not to say that the United States is immune to innovative pricing and contracting. There’s plenty of activity, but it’s often stymied by the practical challenges: is the contract easy to implement (e.g., whether the endpoint around which the contract is constructed can be easily measured, generally through claims data)? The smaller the therapy’s economic impact on the plan, the simpler the deal’s management has to be. Is there an independent third party doing the analytics and financial reconciliation work that the payer doesn’t have time to do and doesn’t trust the pharmaceutical company with? For example, a payer has recently asked us to help with one agreement in which, for an orphan drug, it has had to set up an effect patient registry to track drug discontinuation by a fairly complicated set of timing metrics. That’s a deal that other payers will learn to avoid, unless the pharmaceutical company sets up a third party to do the analytics.

And one category has been particularly resistant to innovative pricing and contracting: oncology. In the first place, CMS significantly curtails any incentives biopharmaceutical
It is certainly possible for a government to have learned a lesson from COVID-19—either buy early and cheap, or buy late and expensive—and apply it to our country’s biggest medical problems.
Getting to simple is no easy task.

Synthesizing complex economic models, methods, and real-world data for healthcare decision makers is what ISPOR’s HEOR news magazine does best.

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