



VALUE & OUTCOMES SPOTLIGHT

A magazine for the global HEOR community.

From the Patients

Defining Patient Engagement in Research

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The Patient Engagement in Research Working Group of the ISPOR Patient-Centered Special Interest Group worked over several years to research and derive consensus on the definition of "patient engagement in research." This group was comprised of patient advocates, academics, industry, and health economic and outcomes research students. The team survived many obstacles that seemed insurmountable on the path to publication, including learning how to conduct a literature review, perform qualitative analysis, and develop consensus.



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The definition published in the June 2020 issue of *Value in Health* is excerpted below:

"The active, meaningful, and collaborative interaction between patients and researchers across all stages of the research process, where research decision making is guided by patients' contributions as partners, recognizing their specific experiences, values, and expertise."

-From [Value in Health](#). Vol. 22, Iss 6.

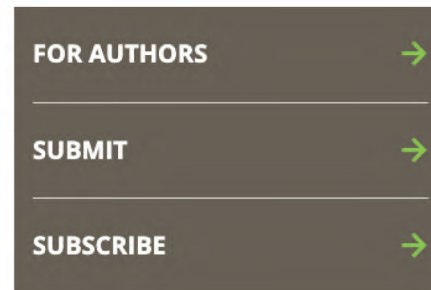
While our definition is easily applicable in health economics and outcomes research, we see potential for it to be used much more broadly. This includes medical research and patients' rights. The definition reflects a broader understanding of truly engaging with participants in a collaborative setting, where the responsibility could be shared by the "sponsor" to include the "one being experimented on" in a full and transparent way.

It's adaptability is its beauty. It applies not only to identifying and interpreting new quality-of-life and patient-reported outcome measures, but also to answering the fundamental questions that need to be considered before the decision to conduct a study has even been taken and the research begins. This includes basic questions such as, "Is this research into a product or area valid?" and "What do patients need?" in any disease or investigative approach. This is why we, the patient researchers, are taking this opportunity to share our thoughts.

Our original hope for the usefulness in defining the term in our report is the same: all healthcare stakeholders can now adopt the underlying principles of the definition and start using it. This definition can also be used to validate organically grown organizational definitions. Patient engagement is frequently subverted into a tool used by many groups to do their "same old, same old" under the guise of being patient centric. Patient engagement has frequently been used as a buzzword. Buzzwords can be taken out of context and molded into things that they really are not meant to be. Organizations can now be asked how their approach differs from the official ISPOR definition of "patient engagement in research." This point of comparison provides a means to hold them accountable to common principles.

On a practical level, we are not introducing a new concept, as much as trying to institutionalize something that has maintained itself on an ethereal level. Rather than a sponsor approaching a group of patients and saying, "This is our research project. Do you like it?", applying the new definition, the approach would be, "You have lymphoma? We research lymphoma. What do you as patients need and how can we accomplish that?"

Through this project we suggest a definition that can be used all along the research pathway. While our definition may seem aspirational, it can be achieved. There are many existing examples of its principles in practice that demonstrate the power of true patient engagement, with patient organizations successfully driving and informing the research process from inception through clinical care. We offer our varied experiences as examples. Each of the following examples resulted in learnings about how to undertake authentic patient engagement in research, as well as the two-way respect and communication during the collaboration can result in an obvious cultural change in both organizations. Our proposed definition reflects these same principles and will hopefully contribute to transformational change in other organizations.



PRO RETINA Deutschland e.V.

The PRO RETINA Deutschland e.V. and its foundation demonstrate the potential of patient organizations in the initiation, acceleration and support of patient-oriented medical research. The foundation aims to identify research needs, partner with research institutes, biomaterial banks, registries, and support patient recruitment for studies. Through patient-initiated and patient-supported research, this organization has achieved the isolation of the choroideremia gene and the development of a retinal implant. The foundation also collaborates on drug approval procedures and other regulatory decision making.

Leber's Hereditary Optic Neuropathy Society

The Leber's Hereditary Optic Neuropathy Society has engaged in patient-focused research and healthcare delivery consortia, which has led to the creation of new patient-originated and patient-directed research networks under the umbrella of the European Joint Project for Rare Diseases. The Leber's Hereditary Optic Neuropathy and the James Lind Alliance engaged in a recent Priority Setting Partnership for primary mitochondrial diseases, which demonstrates the importance of patients and clinicians working together to identify patient-focused research priorities and goals.

The European Organization for Rare Diseases Community Advisory Boards

Many members are familiar with patient advisory boards, typically organized by the sponsor. Community Advisory Boards (eg, the EURORDIS Community Advisory Boards in rare diseases) provide an opportunity for sponsors, mainly pharmaceutical and biotech companies, to collaborate with the patient community throughout the research process. Community Advisory Boards are autonomous bodies not related or chosen by the sponsor and provide valuable input to research protocols through transparent dialogue with researchers and the patient community. Quick wins include changes to research protocols such as revision of inclusion/exclusion criteria, numbers of visits to the clinic during a trial, how many biopsies are needed, the relation of investigational drug to placebos, and much more.

Patient-Focused Drug Development Collaboration

Another example of patient engagement in research is the collaboration between the Accelerated Cure Project's iConquerMS People-Powered Research Network and a life sciences company. This partnership occurred in the lead up to the launch of pivotal clinical trials of a new candidate medicine for relapsing forms of multiple sclerosis. This patient focused drug development Council met monthly to discuss trial design and implementation, clinical trial logistics, patient-reported outcome measures, clinical trial training materials and draft label statements.

As you can see from these few examples, there are different approaches to patient engagement in research. While PRO RETINA focuses mainly on basic and applied research in a university environment, the other examples are primarily focused on clinical trials and public commitment. This is evidence of engagement in "all phases" of research.

"We, the patient representative authors, worked with the health economics and outcomes researchers, showcasing the gravity and importance of including patients in research..."

Looking Ahead to a Patient-Focused Future

While developing this definition, we found the great majority of the existing literature was from scientific articles with minimal input from patients. Our group worked diligently to be as open as possible, considering the perspectives of different users and stakeholder groups. Hats off to all our fellow authors, reviewers, and Special Interest Group and Working Group members who shepherded us through this process. A definition has been produced that can be used and implemented not only by ISPOR, but also can be easily adapted and used in many engagement settings. This includes settings beyond what might be strictly called research where it can benefit society as a whole.

ISPOR has a long-standing commitment to the engagement of patients in healthcare research and decision making worldwide. We, the patient representative authors, worked with the health economics and outcomes researchers, showcasing the gravity and importance of including patients in research, actively listening to patients, and understanding them and their needs and expertise as a stakeholder group. The proposed definition highlights the importance of inclusion, respect, and equality in research. Our hope is that the published article in *Value in Health* can build on the various projects ISPOR has undertaken to include patients in the research and decision-making processes. We hope that this definition will be an aspiration for everyone working in research.

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For more information

Contact patientsig@ispor.org for more information about ISPOR's work with patient engagement.

Patient Engagement in Health Outcomes Research: A Snapshot from the ISPOR Community

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Rachel Harrington

KEY POINTS . . .

Current reported practice of patient involvement in the outcomes research process highlights a lack of bi-directional collaboration, with a potential for missed opportunities.

Findings highlight the lack of consistent methodology for patient engagement and the opportunities to develop a framework to systematically operationalize patient engagement in outcomes research.

The working group is endeavoring to generate recommendations on how to determine the best way to involve patients and their representatives in all stages of research and ensure the effective participation of patients' organizations in the creation and development of tools to measure outcomes.



Introduction

The goal of the ISPOR Patient Centered Special Interest Group is to determine how best to involve patients and their representatives in all stages of decision making, for the purpose of improving health care delivery and outcomes. Within the Special Interest Group, the aim of the Patient Engagement in Research Working Group is to define "patient engagement," and to recommend a framework for successful engagement of patients, health care consumers, and their representatives in the realm of outcomes research and decision making. Toward these goals, a targeted literature review and informal survey of ISPOR members were conducted to generate preliminary data.

The goal of this article is to share the results of this preliminary work, to stimulate further discussions among ISPOR membership and broader stakeholder communities about patient engagement in outcomes research, and to encourage the engagement of patients in outcomes research initiatives.

Targeted Literature Review: Existing Frameworks for Patient Engagement in Research

The working group conducted a targeted literature review to identify existing theoretical frameworks and definitions of patient engagement in health research. Though the review was not all-encompassing, both published and gray literature were examined, representing perspectives ranging from academia, industry, and government, to organizations representing patients. A number of fundamental, consistent conceptual themes of patient engagement were identified [1–5]. Several frameworks described varying levels or intensities of patient engagement in health care and health research [3, 6]. In reviewing these frameworks, the working

group identified three frameworks: 1) Carman et al.; 2) Domecq et al.; and 3) Guise et al., which they found to be helpful in describing patient involvement through the flow of information; the stages of research in which patient engagement occurs; and prioritizing stakeholder engagement in research. The model proposed by Carman and colleagues is bi-dimensional and describes a continuum of engagement characterized by the flow of information between the patient and provider (consultation, involvement, partnership and shared leadership) involvement in direct care, organizational design and governance, and policy making [3]. This hierarchical approach to levels of engagement is also reflected in frameworks created by patient advocacy organizations [6].

Stakeholder engagement has also been examined by "stage" of research (from early development through to dissemination), which can be broadly grouped as preparation, execution and translation [7]. Reviews by Domecq and Guise have examined current practices for engaging stakeholders in research, with Guise particularly focusing on the role of patient engagement in research prioritization [7–8]. Results revealed that patient engagement was reported most often in the early stages of research, particularly in the agenda setting, study design, and recruitment stages. The most consistently and frequently reported engagement activities were interviews, focus groups, and surveys. This suggests that current practice is primarily a one-way communication (consultation) with patients providing information and receiving minimal feedback from the researcher. This lack of bi-directional engagement in current practice is supported by a review of the literature by Domecq and colleagues, who found more collaborative forms of engagement such as deliberation and organizational participation were less frequent across all stages of research [7].

Finally, the working group's review also identified a number of key gaps in evidence, including lack of consistency in the structure of engagement and in its reporting. There is insufficient empirical evidence measuring the impact and success of engagement; no standard method for doing so exists, though a checklist for reporting results of engagement has been proposed [8]. The literature review concluded that there is little structured design or analytical methodology existing around patient engagement.

Survey of ISPOR Membership: Current Perspectives on Patient Engagement in Research

An informal survey on patient engagement was conducted with attendees at two ISPOR conferences: the 19th Annual International Meeting (Montreal, QC, Canada) and the 17th Annual European Congress (Amsterdam, The Netherlands). A total of 39 semi-structured interviews were conducted with a convenience sample (21 in Montreal, 18 in Amsterdam). Working group members used an interview guide developed for the study. The questionnaire included 29 questions, soliciting both closed and open-ended responses, reflecting the following dimensions:

- Definition of patient engagement
- Personal experience with patient engagement, including engagement in:
 - o Data collection
 - o Study design
 - o Interpretation and dissemination of results
 - o Ethics and/or regulatory approval process
- Awareness of patient engagement initiatives at current organization, including:
 - o Engagement objectives and methods
 - o Responsible function(s)
 - o Respondent's own views about existing patient engagement activities
 - o Barriers to engagement
 - o Opportunities and value of engagement
- Views on future directions of patient engagement in organization

Demographic and research setting descriptors with anonymized responses were also collected. Results were analyzed in terms of levels of patient engagement, and by the phases of implementation along the continuum of health outcomes research activities, based on Carman's

framework [3]. These results have been presented at two ISPOR conferences [9-10].

Survey participants represented perspectives from industry (56.4%), health research (17.9%), academia (17.9%), managed care (5.1%), government (2.6%), and clinical practice (2.6%). This distribution was generally representative of the overall ISPOR membership, with some perspectives under-represented (government, health care communications). These results are shown in Table 1. It should be noted that certain fields which may have a significant role in patient engagement, e.g. clinical practice, are not well represented in this sample (nor in the ISPOR membership); this should be taken into account when interpreting and extrapolating from the survey results.

Survey results showed that 84% of participants were aware of some form of patient engagement activities within their organization (data not shown). Participants had limited knowledge about the exact nature of the types of engagement, or hesitated to define patient engagement, with multiple individuals noting that 'this was handled by other groups' within their organization (e.g. patient advocacy/communications groups). When asked to describe patient engagement activities and initiatives, respondents mentioned examples ranging across levels of intensity. Less intensive forms of engagement included 'passive involvement' of patients as research participants in clinical trials, discussing medical needs, consulting on the focus of research, and sharing experiences in clinical trials to discuss ways to enhance recruitment and retention. More intensive forms included patients and patient advocates being co-investigators, actively driving and shaping the research agenda as partners, and leading and funding clinical trials and research. Similar to findings from the literature review, most of the engagement examples mentioned by participants reflected one-way communication from patient to researcher in research organized by the researcher [7-8]. Figure 1 shows results of the survey stratified by phase of research for patient engagement proposed by Domecq et al. [7].

Table 1. Primary work areas of ISPOR informal survey respondents

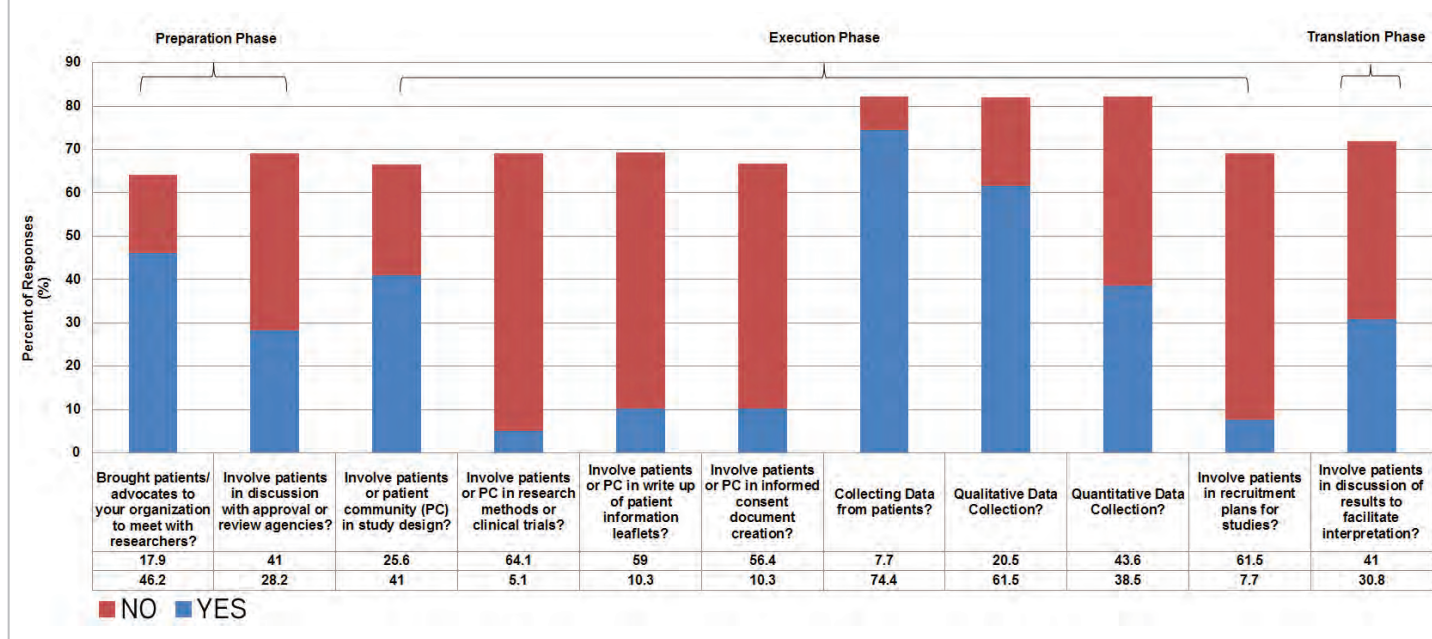
Primary Work Areas	PERWG Survey (N=39)	ISPOR Membership (N=7443)
Industry	22 (56.4%)	3385 (45.5%)
Health Research	7 (17.9%)	1871 (25.1%)
Health Care Communications	0 (0.0%)	334 (4.5%)
Academia	7 (17.9%)	1101 (14.8%)
Managed Care	2 (5.1%)	116 (1.6%)
Government	1 (2.6%)	502 (6.7%)
Clinical Practice	1 (2.6%)	134 (1.8%)

Abbreviation: PERWG indicates Patient Engagement in Research Working Group

Results of the survey aligned with findings from the literature review, particularly with regard to the lack of consistent methodology for patient engagement; no respondents mentioned a specific framework or a standard checklist. However, there was a very strong interest in moving forward and finding ways to systematically operationalize patient engagement in outcomes research.

To put results in context, examples of patient engagement in research mentioned in survey responses are summarized below on a continuum of patient engagement (adapted from Carman), with engagement ranging from consultation (mostly one-way communication) at the basic level, involvement as a middle ground, and partnership and shared leadership being the most intense form of engagement [3]. An example in the consultation level was, "just listening to patient concerns, the impact of the condition, how they're coping, and keeping them interested in the clinical trial." At the involvement level, "part of adherence means patients are involved in their care and are willing participants in finding the best treatment." When asked about personal experience with patient engagement in research, a majority of respondents (66.7%) noted they had engaged patients in their research. However, when probed for specifics, responses focused on patients as research participants, and pointed towards patient involvement in early phases of research (particularly in early clinical research in drug development). One example of patient involvement in early stage research involved "interviews with psoriasis patients to

Figure 1: Survey results on personal experience and patient engagement phases (N=39)



identify unmet needs.” In this case, patient involvement was particularly impactful as it highlighted incorrect assumptions on the part of researchers about which endpoints were most important to patients (initial assumptions were based on general opinion or literature), leading to a change in study endpoints.

In spite of the lack of clarity in how to operationalize patient engagement in health outcomes research, examples were identified that illustrate opportunities worthy of consideration by the research community. Figure 2 summarizes these potential opportunities in context of Carman’s framework.

Future Perspectives for the ISPOR Patient Engagement in Research Working Group

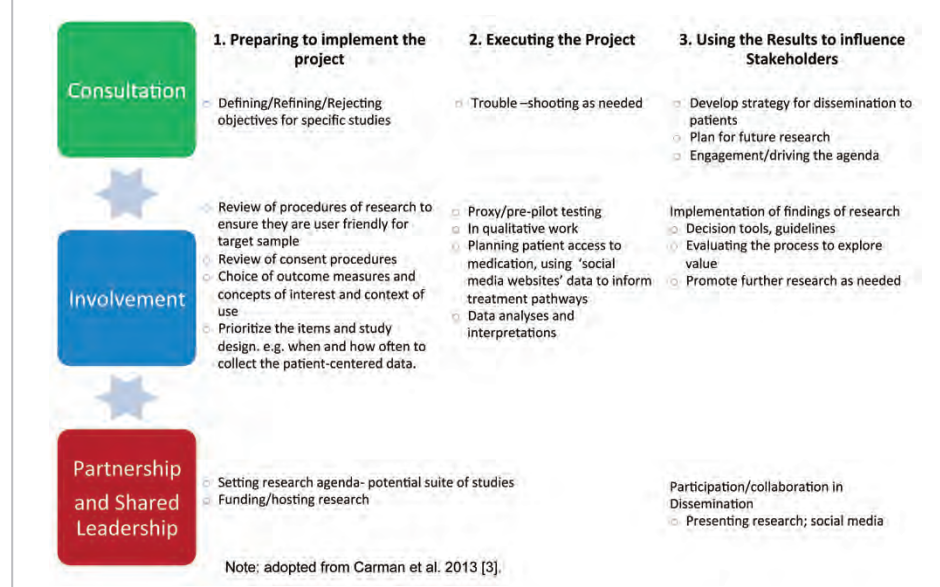
The working group’s goal in executing the targeted literature review and informal survey was to better understand the landscape of patient engagement, particularly with regard to current activity and perspectives for the ISPOR member’s activities involving patient engagement. Though the review was narrowly focused and the survey sample was small, the findings highlight how we can begin to provide some answers for stakeholders. There are opportunities for engaging, consulting, and involving patients within many different stages of health outcomes

research. Within project preparation, involvement may include discussing project objectives with patients or consumers. Gaining this perspective early can be useful in shaping which aspects to emphasize, or helping with priority setting. In project execution, this may include involving patients in the study design process to ensure and optimal approach. Patient input into study design can include consideration of lower participant burden, collection of data within focus groups, development of

interview guides for concept elicitation, and pilot testing of instruments which measure patient experience. Improvements in execution time and energy can be enabled by sharing:

- Details of cognitive interviews with patient advocates
- Patient’s pre-read of protocols prior to project initiation
- Research agenda setting
- Determining funding priorities
- Leading or sponsoring research activities

Figure 2.: Identified opportunities for patient engagement in outcomes research



Patient and researcher alignment toward shared goals provide opportunities to increase project efficiency.

The ISPOR Patient Engagement in Research Working Group recognizes that patient engagement in the context of outcomes research exists along a continuum; starting from activities which involve low levels of intensity (consultation) and moving toward higher levels of intensity (partnership and shared leadership). Timing of engagement is also a factor, with experience suggesting that early engagement may lead to more successful collaborations. When undertaken in the right spirit, this can bring important new insights and in many ways can be regarded as the ultimate “reality check” on the project in hand, which should repay its (relatively small) cost many times over in increased efficiency and can even prove critical to the success of a project. However, if it is skimmed or undertaken in a spirit of tokenism the reverse will often be the result.

It's an exciting time for outcomes researchers, at the threshold of more meaningful engagement with patients, both as partners and co-leaders in research.

Currently, the working group is conducting a systematic literature review to define “patient engagement” for the ISPOR community and its varied stakeholders. The group is endeavoring to generate recommendations on how to determine the best way to involve patients and their representatives in all stages of research (from providing opinions to making decisions), and to ensure the effective participation of patients' organizations in the creation and development of tools to measure outcomes.

Call to Action

Across different settings researchers face challenges to bringing the patient's perspective into drug development and health outcomes research. There is great value however, in understanding this transformational change toward greater patient engagement. It's an exciting time for outcomes researchers, at the threshold of

more meaningful engagement with patients, both as partners and co-leaders in research. The working group welcomes ideas and suggestions from the ISPOR community as it works towards developing best practices to promote consistency, and advance the field of outcomes research. The need for further development of a framework and definition of terms within ISPOR to facilitate patient successful engagement has been identified as critical in the groups' preliminary work. Fostering stakeholders' development of necessary skills and continuous awareness of emerging good practices for patient engagement within the outcomes research community are some of the efforts that can supplement current efforts ongoing within ISPOR. Through collaborative efforts we can demonstrate the value inherent in patient engagement and define new methods to enable its measurement. Much work remains and help from all interested stakeholders is needed to improve clarity in capturing stakeholder perspectives and to identify gaps and future needs for research in this area.

Acknowledgements

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Additional information:

The following article is based on a workshop, “Patient Engagement in Outcomes Research: Current Status, Questions, Beliefs, and Future Perspectives”, presented at the ISPOR 17th Annual European Congress in Amsterdam, The Netherlands. The Patient Centered Special Interest Group was formed after the first ISPOR Patient Representative Roundtable met in Dublin and requested a multi-stakeholder group including patient representatives be developed to address issues to engage patients in the research process.

To view the presentation, go to: <http://www.ispor.org/sig/PatientCentered/WorkshopPresentation-2014Amsterdam.pdf>

To learn more about the ISPOR Patient Centered Special Interest Group, go to: http://www.ispor.org/sigs/PatientCentered/PC_EngagementInResearch.aspx




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FROM THE EDITORS

It is our distinct honor to serve as the new Editors-in-Chief of *Value & Outcomes Spotlight*. We would like to express our gratitude to David Thompson for his exceptional dedication and leadership as Editor-in-Chief for the past 12 years. David and the ISPOR editorial staff established *Value & Outcomes Spotlight* as the premier HEOR (health economics and outcomes research) news magazine, and upon that solid foundation, we will build the next generation global news outlet for HEOR. We will do so by combining our experiences in academia and industry—both at a US and global level—to present methodological topics in HEOR with fresh, virtual, and engaging content to attract a broader and more diverse readership.

As we turn the page to the next chapter of *Value & Outcomes Spotlight*, we commit to delivering a publication that both provides relevant content and resonates with both HEOR experts and non-experts. We pledge that topics covered in the magazine will be timely and impactful to a broad range of healthcare disciplines and audiences. In the maelstrom of a global pandemic, growing societal demands, and ever-increasing pressures on the healthcare infrastructure, understanding and leveraging the principles of HEOR by a broader audience of patients, government entities, and private healthcare sponsors will be even more critical. Now more than ever, clearly and broadly communicating the impact and value of HEOR to inform decisions regarding healthcare treatments is essential. As HEOR data and methods become even more widely applicable and increasingly more sophisticated, clearly conveying our methodologies and principles to this broader audience will better facilitate their uptake and practice.

The current news era of multimedia outlets, questionable truths, and “belief” over “fact” demands that the content of our publication resonates with our readers. The publication's digital format will provide opportunities to reach new audiences yet present new challenges and opportunities as we compete with a multitude of virtual content that debates the complex intertwine of healthcare costs, cost-effectiveness, policies, and assessments. Resonating with our readership will demand that our content rise above the day-to-day noise of these virtual outlets by providing relevant, insightful, and fact-based perspectives on HEOR. We will leverage ISPOR's world-renowned reputation and resources, together with newly integrated modern communication platforms, to attract a broader audience of readers. Providing innovative virtual content that resonates with our readership will also be necessary to successfully establish our presence and differentiate our voice in a world that is operating almost entirely virtually.

Ultimately, you—our contributors and readers—will define the relevance and resonance of the magazine's future. We welcome your ideas, input, and feedback to help shape the content and maintain the high quality of *Value & Outcomes Spotlight*. On behalf of the editorial staff and ISPOR, thank you for your loyal readership and contributions to *Value & Outcomes Spotlight* and to the Society.

Semper ad meliora!

Zeba M. Khan, RPh, PhD and
Laura T. Pizzi, PharmD, MPH
Editors-in-Chief,
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ISPOR SPEAKS

Setting a Course for the Future in Our New Economic Reality

Jens Grueger, PhD, ISPOR President 2020-2021, Director and Partner, Boston Consulting Group, Zurich, Switzerland

I have assumed my role as President of ISPOR at the beginning of July, at a time when the daily number of people newly infected with COVID-19 has reached new highs, with more than 12 million people infected and more than half a million deaths globally. I want to thank you all for the trust that you put in me to lead ISPOR during these challenging times.

I joined ISPOR in 1999, more than 20 years ago, as member #3201. That year, I started my new role as Head of Global Health Economics at Novartis. Diana Brixner, ISPOR President 2007-2008, was my colleague leading the Novartis US Health Economics team. Lou Garrison, ISPOR President 2016-2017, was leading health economics at Roche on the other side of the river, and Rob Epstein, who I collaborated with at Merck and Medco, was the ISPOR President at the beginning of that year. I was excited to be in the same company with all of these people and many more at ISPOR...it was my entrance to the global health economics and outcomes research (HEOR) community and connection to state-of-the-art HEOR methods.

I have attended all European ISPOR conferences and many US conferences in North America since then. I have seen these meetings grow from less than 1000 to over 5000 people. I liked the small meetings, where you could meet practically everyone who attended, and I have come to like the large meetings with their amazing spectrum of plenaries, methods sessions, issues panels, and workshops. I was proud to be elected to the Board of Directors from 2004-2006 and to be invited to speak in the plenary sessions in the 2009 and 2013 European meetings. I particularly enjoyed the work on the real-world evidence and performance-based risk-sharing agreements taskforces.

Today, ISPOR is more important and relevant to people in academia,

industries, and healthcare than ever before. All of us coming together in ISPOR are passionate about informing better decisions to improve health outcomes for people around the world in a way that is financially sustainable. We are living in exciting and challenging times where science offers us previously unimaginable opportunities with cell and gene therapies, amazing diagnostic capabilities like molecular profiling and high-resolution imaging, and digital apps, and biomarkers. We realize that in order for health systems to pay for this, we need better information and rapid exchange of our perspectives and insights: new evidence, new methods, new models, new practices, and governance. And we need platforms where all stakeholders can come together.

COVID-19 is a turning point in how we value health and organize healthcare. In our ISPOR value flower (Figure), we have explicitly considered risk of contagion, which has been considered as a value element before, and fear of contagion as a new value element. At the same time, we realize that while the societal value of new therapeutics that prevent the spread and reduce the morbidity from the disease is huge, pharma companies will be expected to price their products substantially below that value given the financial constraints of countries.

We all agree how important it is to bring together real-time data and evidence in value-based healthcare systems that optimize for outcomes that are relevant for patients and for cost. We have seen changes in how societies accept and use digital tools to get better information and control of the spread of the disease. We have realized that we cannot optimize only for efficiency in a static way. Instead, we need to optimize the use of resources to drive innovation and eliminate redundancies to deal with catastrophic events.



We have all been working from home for many months, and we have become experts in using conferencing systems, online shops, and digital health services, including telehealth. We are at the beginning of a new era of working, communicating, and interacting with each other. Coming together in large events and conferences, like our ISPOR conferences, will remain important, but we will have more variety in how we come together that does not always require physical presence and travel.

When I wrote my vision statement to apply for the role of ISPOR President last year, I did not foresee COVID-19. I was focusing on 3 areas, all of which I believe are even more relevant now:

1. Ensure our HEOR methods and procedures are keeping pace with the move towards an increased people-centric focus on health and well-being, new and more complex healthcare technologies, and the availability of vast sources of digital data and advanced analytics. As we follow the science in understanding biology and diseases, we will discover more complex healthcare technologies that will increasingly combine diagnostics, preventive services, treatments, and outcome monitoring, targeting ever smaller patient populations in a much more personalized (sometimes even individualized way) to produce transformative outcomes for patients and potentially even avoid/cure

diseases. While our value frameworks and evidence tools are flexible and cover a broad range of perspectives and data sources, their application and interpretation require new tools and approaches. In addition, we will see HEOR increasingly being applied at a systems level, specifically in the context of value-based healthcare and value-based insurance design. This will be facilitated by better availability, quality, and interoperability of real-world data—from electronic health records, hospital information, pharmacy, and lab systems all the way to sensors and wearables

2. Take a truly global perspective to ensure that HEOR information leads to better decisions about healthcare, in particular as we see a shift in developing economies around the world towards noncommunicable diseases that require new capabilities and more capacity in HEOR and HTA. We will have to find ways to

make HEOR and HTA more efficient, fostering collaboration and sharing of work between authorities, avoiding duplication and providing high-quality competent input in capacity-constrained environments. At the same time, it needs to be tailored to the respective health systems and health problems and integrated into the broader policy context and priorities.

3. Strengthening our leadership pipeline and providing a clear path for the talented people that come to ISPOR to engage in the society and become the future leaders of this organization. Many of you have already contacted me and expressed your interest in serving the society more. In my time on the Nominations Committee, I observed that we do not have broad visibility of all the people that are already working in our various committees, chapters, and interest groups, and we can do better in

coaching and guiding our younger colleagues on how they can engage and grow in the organization.

I hope these goals resonate with you, and I am optimistic and committed to make tangible progress on each of these over the next 12 months.

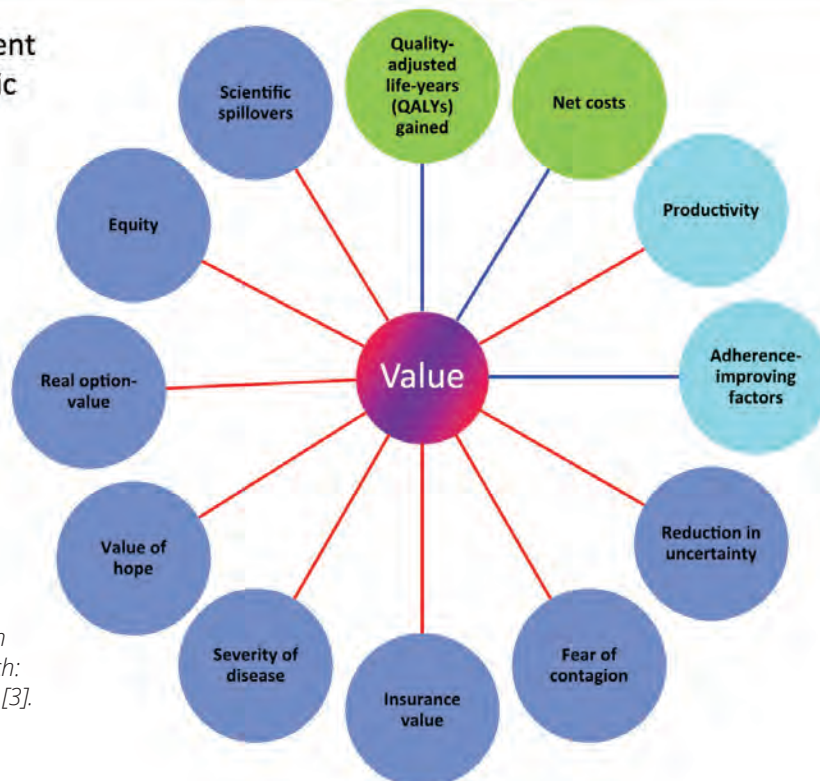
Of course, on top of this, I will work closely with CEO Nancy Berg, the ISPOR staff, the Board of Directors, and the Past Presidents Council to make sure that ISPOR continues on a promising path that adapts to the new realities of scientific societies and conferences in times of the pandemic, using digital technologies in a much more profound way and ensuring a positive financial outlook for the society.

Thank you again for your trust and support, and all the best to you and your families. Stay healthy. •

Elements of Value

Challenge: Map each element into an underlying economic framework for value assessment.

Note. Green circles: core elements of value; light blue circles: common but inconsistently used elements of value; dark blue circles: potential novel elements of value; blue line: value element included in traditional payer or health plan perspective; and red line: value element also included in societal perspective. [Source: Defining Elements of Value in Health Care—A Health Economics Approach: An ISPOR Special Task Force Report [3]. Value Health. 2018;21(2):131-139.]



HEOR NEWS

1 COVID-19 and Remdesivir: Rethinking How We Measure a Drug's "Value" (STATnews)

Remdesivir, Gilead Sciences' repurposed antiviral drug, offers the first opportunity to figure out what is an appropriate pricing approach—and price—for emerging therapies, say Patricia Deverka, Louis Garrison, and Samuel Nussbaum of the Innovation and Value Initiative in a June 15 opinion piece for STAT. The authors say the organization "has a number of concerns about the process and substance of the analyses" done by the Institute for Clinical and Economic Review (ICER) on remdesivir. [Read more.](#)

2 Global Regulators Discuss Data Requirements for Phase III Trials of COVID-19 Vaccines (Pharma Focus Asia)

Many researchers around the world are currently working on vaccines against COVID-19 but a rapid authorization of COVID-19 vaccines will only be possible if robust and sound scientific evidence on vaccine candidates' quality, safety, and efficacy is generated. International convergence of data requirements is intended to encourage and accelerate the development of vaccines as a global public health good.

[Read more.](#)

3 New Journal Will Vet COVID-19 Preprints, Calling Out Misinformation and Highlighting Credible Research (STAT)

MIT Press in June announced the launch of an open access journal, *Rapid Reviews: COVID-19*, that will publish reviews of preprints related to COVID-19, in an effort to quickly and authoritatively call out misinformation as well as highlight important, credible research. The journal will use an artificial intelligence system developed at Lawrence Berkeley National Laboratory to categorize new preprints by discipline (such as epidemiology or clinical care) and degree of novelty.

[Read more.](#)

4 Alternative Policies for Pricing Novel Vaccines and Drug Therapies for COVID-19 (ICER)

In a white paper, ICER's Sarah K. Emond, MPP, and Steven D. Pearson, MD, MSc, examine the issues of pricing for COVID-19 vaccines and therapies. According to the authors, the paper is intended as a short introductory overview to inform public and policymaker discussions regarding the best way to harness public and private efforts to achieve rapid, equitable, and affordable treatment for COVID-19 in the United States.

[Read more.](#)

5 Insurance Denials of Care Amount to Unlicensed Medical Practice (*Journal of Managed Care & Specialty Pharmacy*)

In an editorial in the July 1 *Journal of Managed Care & Specialty Pharmacy*, William E. Bennett, MD, MS, expresses his frustration with insurance denials of care. This practice, he argues, "is directly harmful to patients and the healthcare system because

it (a) amounts to an unqualified entity practicing medicine with limited information about the patient, (b) does not actually contain costs, and (c) is not an effective method to improve care quality...when the payer is in the position to make these decisions, often unilaterally, their inherent bias to lower cost will always dominate. So, to pretend that this is being done for the benefit of patients clearly rings false."

[Read more.](#)

6 Economists and Epidemiologists Not at Odds but in Agreement: We Need a Broad-Based COVID-19

Testing Survey (Johns Hopkins Coronavirus Resource Center)

Economists and epidemiologists at Johns Hopkins say in an op-ed that tackling the COVID-19 pandemic in the United States will require thoughtful collaboration, not conflict, between public health and economics professionals. "In short, epidemiologists and economists, jointly pursuing the well-being of the US populace, must rapidly learn to join hands in providing appropriate guidance to our nation's leaders as to how to weather the current pandemic," the authors say. "What they both desperately need is data that can help them sort out the next rounds of policy in this terribly difficult time."

[Read more.](#)

7 Comparison of Health Technology Assessments and Time to Reimbursement for Orphan Drugs (European Pharmaceutical Review)

This article delves into 4 health technology assessment agencies, reviewing a study that analyzes the opportunities and challenges for orphan drugs in France, Germany, England, and Scotland. The authors found that despite several regulations and concessions to support better outcomes for drugs, reimbursement assessments are inconsistent across the EU markets included in this study. As a result, manufacturers continue to face access challenges.

[Read more.](#)

8 Competitive Orphan Drug Market Will Drive Down Prices, OptumRx Predicts (FiercePharma)

Developers of orphan drugs will no longer enjoy free rein when it comes to pricing, OptumRx says, for the simple reason that many of the near-term product releases will be entering crowded markets.

[Read more.](#)

9 ICER Reschedules Cystic Fibrosis Public Meeting for August 27, 2020 (ICER)

ICER moved its public meeting to discuss the comparative clinical effectiveness and value of treatments for cystic fibrosis to August 27, 2020. The public meeting, previously postponed due to the COVID-19 pandemic, will be held virtually. The Evidence Report will be subject to deliberation during this public meeting of the California Technology Assessment Forum, one of ICER's 3 independent evidence appraisal committees.

[Read more.](#)

10 Financing Drug Innovation in the United States: Current Framework and Emerging Challenges

(Pharmacoeconomics)

This paper reviews the main elements of the current US system for financing drug innovation and its approach to balancing multiple objectives. Continued experimentation and the input of a range of stakeholders are needed to ensure next-generation therapeutic advances continue to be developed and made available to patients.

[Read more.](#)

11 The Things You Need to Know About the Digital Transformation of Primary Research

(PRMA Consulting)

Sophie Clayton-Welch, Head of the International Experts Group at PRMA Consulting, discusses 3 ways that new technology is helping market access professionals gain cost-effective, real-time payer insight: quality, speed, and compliance.

[Read more.](#)

12 Clinical and Economic Outcomes Evaluated in Lyme Disease: A Systematic Review

(Parasites & Vectors)

The financial implications of Lyme disease can vary widely for both the health system and the individual patients experiencing the disease. The aim of this review was to summarize published data on clinical and economic outcomes associated with Lyme disease. The most frequent costs identified focused on formal health costs, and productivity losses were the most common costs identified outside of the health system.

[Read more.](#)



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RESEARCH ROUNDUP

Section Editor: **George Papadopoulos**, Emerald Corporate Group Pty Ltd, Sydney, Australia

Traditionally, approaches to consumer behavior have been influenced by standard economic theory and models. These are based on the assumption of human rationality. Behavioral economics draws on psychology and the behavioral sciences in assessing consumer behavior. This approach postulates that consumers are subject to a range of psychological biases and use various heuristics such as rules-of-thumb, or educated guesses, when making choices. More simply stated, behavioral economics applies economic and psychological principles to overcome barriers to behavior change.

We have identified 4 research papers that encapsulate these characteristics and are worth reading. We, as always, trust you enjoy delving into the research area of behavioural economics and look forward to highlighting new research in the next edition.

Behavioral Experiments in Health Economics

Galizzi M M, Wiesen D.

Oxford Research Encyclopedia, Economics and Finance.

Oxford Univ. Press.2018; <http://dx.doi.org/doi/10.1093/acrefore/9780190625979.013.244>. Accessed July 9, 2020

Summary

The state-of-the-art literature at the interface between experimental and behavioral economics and health economics is reviewed by identifying and discussing 10 areas of potential debate about behavioral experiments in health. The authors review these areas by posing 10 questions to explore these areas and then answer these questions systematically, in a very thorough manner and well referenced.

By using this framework, the authors review the different streams and areas of application of the field of behavioral experiments in health by discussing which significant questions remain to be discussed, and by highlighting the rationale and the scope for the further development of behavioral experiments in health in the years to come.

Relevance

A long read to begin the research round-up, but the paper reviews the state of the art of behavioral experiments in health by critically discussing the 10 key areas of potential debate and misconception by highlighting their theoretical and empirical rationale and scope, and by discussing the significant questions that remain.

Using Behavioral Economics to Encourage Parent Behavior Change: Opportunities to Improve Clinical Effectiveness

Jenssen B P, Buitenheim A M, Fiks A G.

Acad Pediatr. 2019;19(1): 4–10.

<http://dx.doi.org/doi/10.1016/j.jacap.2018.08.010>

Accessed July 9, 2020

Summary

Pediatric clinical practice often involves improving child health by changing parents' behavior. The application of these approaches to parent behavior change in pediatric settings has the potential to improve the clinical effectiveness of child healthcare. The

authors review the foundational concepts of behavioral economics and identify the unique role of pediatricians in motivating parent behavior change. The authors highlight 4 key behavioral economics strategies that may now be applied more broadly in clinical practice to promote parent behavior change and to support parent decision making to improve child health. The 4 key strategies in practice are message framing; the use of defaults; enhanced active choice; and leveraging social forces.

Relevance

Leveraging behavioral economic principles around parental decision making has the potential to enhance program effectiveness and improve patient and family health.

User-Centered Development of a Behavioral Economics Inspired Electronic Health Record Clinical Decision Support Module

Chokshi S K, Troxel A, Belli H, et al.

Stud Health Technol Inform. 2019;264:155–1158.

<http://dx.doi.org/10.3233/SHT1190407>. Accessed July 9, 2020

Summary

Changing ingrained physician behaviors is difficult and integrating behavioral economic strategies into electronic health records using various clinical decision support tools is a novel approach to improving guideline adherence that also seeks to minimize negative impacts on clinical workflow and cognitive load. This study employed a pragmatic, with an emphasis on real-world clinical workflows, a user-centered approach to develop a new behavioral economics-inspired clinical decision support module to improve provider adherence to guideline targeting over-treatment among older adults with diabetes. The resulting behavioral economics-electronic health records module established a platform for exploring the ability of behavioral economics concepts embedded within the electronic health records to affect guideline adherence for Choosing Wisely target areas.

Relevance

The resulting behavioral economics-electronic health records module establishes a platform for exploring the ability of behavioral economics concepts embedded within the electronic health record to affect guideline adherence for other

Choosing Wisely target areas. This represents an interesting and new channel for influencing provider behavior through less cognitively burdensome methods. Evidence and lessons learned from this study can potentially inform the design, testing, and implementation of similar interventions for other target conditions.

Behavioral Economics Interventions in Clinical Decision Support System

Insook Cho I, Bates D W.

Yearb Med Inform 2018;114-21. <http://dx.doi.org/10.1055/s-0038-1641221>. Accessed July 9, 2020

Summary

Clinical decision support systems can improve safety and facilitate evidence-based practice. However, clinical decisions are often affected by the cognitive biases and heuristics of clinicians, which is increasing the interest in behavioral and cognitive science approaches in the medical field. The authors found the following 5 behavioral economics concepts have frequently been considered in clinical decision support studies: social norms, framing effect, status-quo bias, heuristics, and overconfidence bias. The authors introduce applications and example studies related to each concept.

Relevance

The authors revealed that the use of behavioral economics techniques is increasing in areas such as antibiotics prescribing and preventive care. Clinical decision support systems have the potential to change the way medicine is taught, since responding to them well will become a key skill. •

FROM THE JOURNALS

Validity and Responsiveness of Preference-Based Quality-of-Life Measures in Informal Carers: A Comparison of 5 Measures Across 4 Conditions

Value Health. 2020;23(6):782-790

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

Caregiver burden can be a significant problem for diseases that affect the very young or elderly. Hence therapies that improve those conditions could improve quality-of-life (QoL) of patients as well as their carers. However, quantifying caregiver burden has been traditionally difficult. Large prospective observational studies investigate and quantify costs and resource use for Alzheimer's disease (eg, GERAS study). The QoL side of the burden is more challenging where, perhaps outside of Alzheimer's disease, little preference-based information exists and there is also an uncertainty about which methods are best.¹

There are a number of quality of life measures used to assess informal carers' QoL: the ICEpop CAPability measure for Adults (ICECAP-A) is generic QoL measure that can pick up care-related and HRQoL issues; specifically care-related QoL measures include the Carer Experience Scale (CES), the CarerQoL-7D, and the Adult Social Care Outcomes Toolkit for Carers (ASCOT-Carer) are designed for use in economic evaluations and set of preference weights have been generated in a number of countries. Of course, the EQ-5D-5L is also an option to measure the HRQoL of caregivers.

The authors of the paper set out to examine the performance of the above measures in terms of construct validity and responsiveness. They conducted a *de novo* study including informal caregivers for patients across five prevalent diseases that often require informal caregiver support: dementia, stroke, mental illness, and rheumatoid arthritis.

A sample of informal caregivers were drawn from three waves of the UK Family Resources Survey, between 2013 and 2016. The authors created a conceptual mapping of the QoL measures. They used that to create a survey that provided a structured framework that the measures can be assessed against. These constructs were grouped into

three categories: the carer, the care recipient, and the caring situation. The latter included the extent of the care per week, the relationship between the carer and caregiver, among others.

Participants were invited to fill in a baseline survey and followed up at 12 months. Follow-up was dependent on the care situation: if someone stopped care for the baseline care recipients, they were asked to complete the 2 generic QoL measures 12 month post baseline; participants who remained in the caring role were asked to complete all QoL measures and contextual questions related to the carer, the care recipient, and the caring situation.

Overall, 576 carers responded to the baseline survey, mostly female (65%), mean age of 62 (SD=11); 46% caring for a parent and 35% for a partner; care recipients were on average 74. The QoL surveys At follow-up, QoL surveys were filled by 314 (75%) patients, with high completion rate (96-98%). Construct validity was tested based on prespecified evidence-based hypotheses. Responsiveness was evaluated using two anchor variables: the HRQoL of the care recipient and the hours of informal care provided. The level of these variables at baseline and follow-up were compared, and the change in QoL outcome was examined for three groups: those who stayed at the same level, those whose situation improved (recipient's QoL improved, or hours of care reduced) or who had a decline in the situation.

Construct validity was stronger for the ASCOT-Carer and in ICECAP-A than the other measures. In terms of responsiveness only small changes were seen for both anchors, therefore results were mixed: CarerQoL-7D may be more responsive than CES or ASCOT-Carer, but none of the measures exhibited large responsiveness. This is potentially attributable to the sample in the study: most participants had been in the same

role for many years, on average for 10 years.

As one of the main conclusions, the authors pointed out that measures that focusing on a broader set of outcomes beyond just health of the carers were more sensitive than the EQ-5D. However, the authors suggest that EQ-5D does have an encouraging level of validity.

The results of this study provide good evidence of the validity and mixed evidence of responsiveness of the care related and generic QoL measures for informal carers of adults suffering from 4 highly prevalent conditions that are associated with diverse impacts on carers' lives. The paper provides a rich set of results that will be helpful for health researchers trying to identify and select measures to be included in studies to measure caregiver quality of life, potentially providing information for economic evaluation. The study focussed on diseases affecting the elderly. Therefore, it would be interesting to understand the applicability of its findings to situations where the recipient is a child. •

References

1. Reed C, Happich M, Argimon JM, et al. What drives country differences in cost of Alzheimer's disease? An explanation from resource use in the GERAS study. *J Alzheimers Dis.* 2017;57(3):797-812. doi: 10.3233/JAD-160449.

Defining Patient Engagement in Research

Rob Camp, BS, Community Advisory Board Programme, EURORDIS, Barcelona, Spain; **Russell Wheeler, BSc**, Leber's Hereditary Optic Neuropathy, Merusac, France; **Rainald von Gizycki, MA, PhD**, PRO RETINA Deutschland e.V., Aachen, Germany; **Robert McBurney, BSc, PhD**, Accelerated Cure Project for Multiple Sclerosis, Waltham, MA, USA

The Patient Engagement in Research Working Group of the ISPOR Patient-Centered Special Interest Group worked over several years to research and derive consensus on the definition of "patient engagement in research." This group was comprised of patient advocates, academics, industry, and health economic and outcomes research students. The team survived many obstacles that seemed insurmountable on the path to publication, including learning how to conduct a literature review, perform qualitative analysis, and develop consensus.

The definition published in the June 2020 issue of *Value in Health* is excerpted below:

"The active, meaningful, and collaborative interaction between patients and researchers across all stages of the research process, where research decision-making is guided by patients' contributions as partners, recognizing their specific experiences, values and expertise."¹

From *Value in Health*, Vol. 23, Issue 6

While our definition is easily applicable in health economics and outcomes research, we see potential for it to be used much more broadly. This includes medical research and patients' rights. The definition reflects a broader understanding of truly engaging with participants in a collaborative setting, where the responsibility could be shared by the "sponsor" to include the "one being experimented on" in a full and transparent way.

It's adaptability is its beauty. It applies not only to identifying and interpreting new quality-of-life and patient-reported outcome measures, but also to answering the fundamental questions that need to be considered before the decision to conduct a study has even been taken and the research begins. This includes basic questions such as, "Is this research into a product or area valid?" and "What do patients need?" in any disease or investigative approach. This is why we, the patient researchers, are taking this opportunity to share our thoughts.

Our original hope for the usefulness in defining the term in our report is the same: all healthcare stakeholders can now adopt the underlying principles of the definition and start using it. This definition can also be used to validate organically grown organizational definitions. Patient engagement is frequently subverted into a tool used by many groups to do their "same

old, same old" under the guise of being patient centric. Patient engagement has frequently been used as a buzzword. Buzzwords can be taken out of context and molded into things that they really are not meant to be. Organizations can now be asked how their approach differs from the official ISPOR definition of "patient engagement in research." This point of comparison provides a means to hold them accountable to common principles.

On a practical level, we are not introducing a new concept, as much as trying to institutionalize something that has maintained itself on an ethereal level. Rather than a sponsor approaching a group of patients and saying, "This is our research project. Do you like it?", applying the new definition, the approach would be, "You have lymphoma? We research lymphoma. What do you as patients need and how can we accomplish that?"

Through this project we suggest a definition that can be used all along the research pathway. While our definition may seem aspirational, it can be achieved. There are many existing examples of its principles in practice that demonstrate the power of true patient engagement, with patient organizations successfully driving and informing the research process from inception through clinical care. We offer our varied experiences as examples. Each of the following examples resulted in learnings about how to undertake authentic patient engagement in research, as well as the two-way respect and communication during the collaboration can result in an obvious cultural change in both organizations. Our proposed definition reflects these same principles and will hopefully contribute to transformational change in other organizations.

PRO RETINA Deutschland e.V.

The PRO RETINA Deutschland e.V. and its foundation demonstrate the potential of patient organizations in the initiation, acceleration and support of patient-oriented medical research. The foundation aims to identify research needs, partner with research institutes, biomaterial banks, registries, and support patient recruitment for studies. Through patient-initiated and patient-supported research, this organization has achieved the isolation of the choroideremia gene and the development of a retinal implant. The foundation also collaborates on drug approval procedures and other regulatory decision making.

Leber's Hereditary Optic Neuropathy Society

The Leber's Hereditary Optic Neuropathy Society has engaged in patient-focused research and healthcare delivery consortia, which has led to the creation of new patient-originated and patient-directed research networks under the umbrella of the European Joint Project for Rare Diseases. The Leber's Hereditary

Optic Neuropathy and the James Lind Alliance engaged in a recent Priority Setting Partnership for primary mitochondrial diseases, which demonstrates the importance of patients and clinicians working together to identify patient-focused research priorities and goals.

The European Organization for Rare Diseases Community Advisory Boards

Many members are familiar with patient advisory boards, typically organized by the sponsor. Community Advisory Boards (eg, the EURORDIS Community Advisory Boards in rare diseases) provide an opportunity for sponsors, mainly pharmaceutical and biotech companies, to collaborate with the patient community throughout the research process. Community Advisory Boards are autonomous bodies not related or chosen by the sponsor and provide valuable input to research protocols through transparent dialogue with researchers and the patient community. Quick wins include changes to research protocols such as revision of inclusion/exclusion criteria, numbers of visits to the clinic during a trial, how many biopsies are needed, the relation of investigational drug to placebos, and much more.

Patient-Focused Drug Development Collaboration

Another example of patient engagement in research is the collaboration between the Accelerated Cure Project's iConquerMS People-Powered Research Network and a life sciences company. This partnership occurred in the lead up to the launch of pivotal clinical trials of a new candidate medicine for relapsing forms of multiple sclerosis. This patient focused drug development Council met monthly to discuss trial design and implementation, clinical trial logistics, patient-reported outcome measures, clinical trial training materials and draft label statements.

As you can see from these few examples, there are different approaches to patient engagement in research. While PRO RETINA focuses mainly on basic and applied research in a university environment, the other examples are primarily focused on clinical trials and public commitment. This is evidence of engagement in "all phases" of research.

Looking Ahead to a Patient-Focused Future

While developing this definition, we found the great majority of the existing literature was from scientific articles with minimal input from patients. Our group worked diligently to be as open as possible, considering the perspectives of different users and stakeholder groups. Hats off to all our fellow authors, reviewers, and Special Interest Group and Working Group members who shepherded us through this process. A definition has been produced that can be used and implemented not only by ISPOR, but also can be easily adapted and used in many engagement settings. This includes settings beyond what might be strictly called research where it can benefit society as a whole.

ISPOR has a long-standing commitment to the engagement of patients in healthcare research and decision making worldwide. We, the patient representative authors, worked with the health economics and outcomes researchers, showcasing the gravity and importance of including patients in research, actively listening to patients, and understanding them and their needs and expertise as a stakeholder group. The proposed definition highlights the importance of inclusion, respect, and equality in research. Our hope is that the published article in *Value in Health* can build on the various projects ISPOR has undertaken to include patients in the research and decision-making processes. We hope that this definition will be an aspiration for everyone working in research. •

Reference

1. Harrington RL, Hanna ML, Oehrlein E, et al. Defining Patient Engagement in Research: Results of a Systematic Review and Analysis: Report of the ISPOR Patient-Centered Special Interest Group. *Value Health*. 2020;23(6): 677-688.

For more information

Contact patientsig@ispor.org for more information about ISPOR's work with patient engagement.

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Jointly sponsored by ISPOR and the US Food and Drug Administration (FDA) Center for Devices and Radiological Health (CDRH), this Summit titled **Using Patient-Preference Information in Medical Device Regulatory Decisions: Benefit-Risk and Beyond**, will focus on medical devices and the use of patient-preference information (PPI) in regulatory and other decision-making processes.

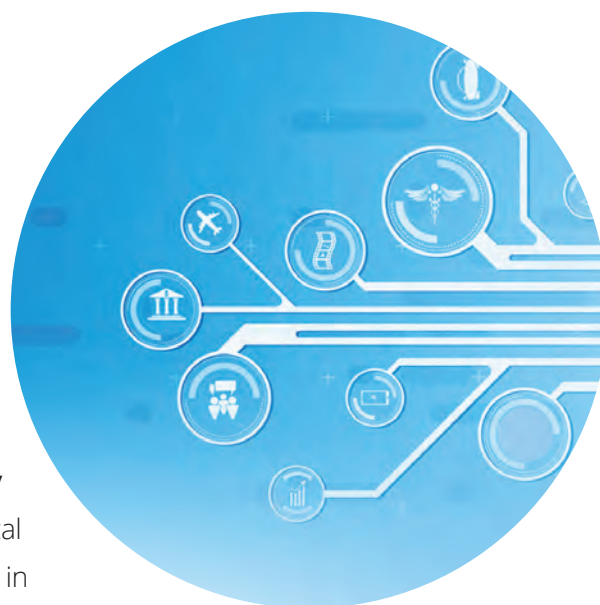
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- The value of including PPI in regulatory, reimbursement, and patient-provider decision-making processes

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At the start of a new decade in the shadow of a global pandemic, the questioning of fundamental conventions around value, risk, rewards, and the role of public and private sectors has never been more relevant. The theme for the European conference, **Improving Health: Establishing Incentives and Sharing Value**, will be reflected through a variety of educational sessions, including three plenary sessions:

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- Much Ado About Little: Dealing with Limited RCT Evidence for Early HTA and Reimbursement Decisions

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WELCOME

Assigning Authorship of Scholarly Publications: Guidance and Resources in HEOR

Steve Crow, MS, ELS

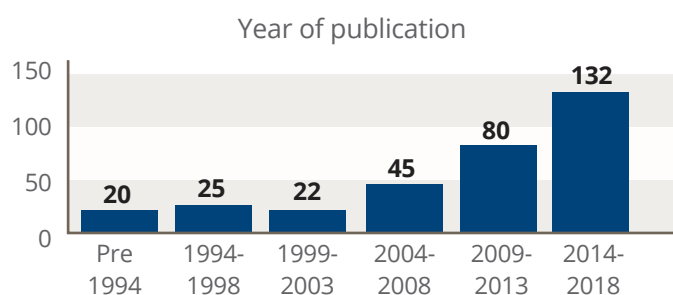
A commentary in the current issue of ISPOR's Value in Health and an editorial in response highlight the importance of properly assigning authorship in scholarly publications. These contributions bring to mind established authorship guidance that has been provided by organizations across the publishing landscape. This article reviews core components of longstanding authorship recommendations within scholarly publishing generally and specific guidance in the field of health economics and outcomes research.

Introduction

Proper acknowledgement of authorship is a key component of normative scholarly conduct. Indeed, the "designation of authorship is essential for published research to be represented by those who provide significant intellectual contribution to its development and execution."¹

While discussions regarding legitimate authorship assignment date back for centuries, the topic has seen a rapid escalation in the published research over the past dozen years. For example, in their 2020 literature review on ethical issues related to scientific authorship, Hosseini and Gordijn identified and analyzed 324 eligible articles. Of those, nearly two-thirds (212) had been published just since 2009 (Figure 1).²

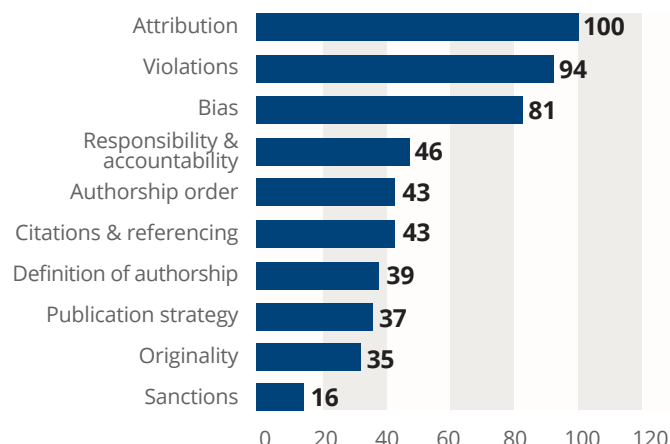
Figure 1. Year of publication of documents considered for analysis of ethical issues related to scientific authorship



(Source: Hosseini M, Gordijn B. A review of the literature on ethical issues related to scientific authorship. *Accountability in Research*, 27:5, 284-324.) Used with permission

Furthermore, their review categorized and ranked the 10 top authorship issues as indicated by the frequency of their occurrence in the literature. As shown in Figure 2, the top 3 issues stand apart numerically. The 3rd most commonly cited issue, bias, includes conflicts of interest (both financial and non-financial), biased use of language, biased interpretation of results, biased visual depictions, and gender bias. The 2nd most cited issue, violations of the norms of authorship, relates to both serious violations including fabrication, falsification, and plagiarism as well as questionable practices such as self-citation or exploiting subordinates to publish more. But the most frequently mentioned theme was attribution, relating to "factors that should be considered in recognizing contributors' efforts and confirming their contributions to publications."²

Figure 2: Ethical issues ranked on the basis of their occurrence in the literature



(Source: Hosseini M, Gordijn B. A review of the literature on ethical issues related to scientific authorship. *Accountability in Research*, 27:5, 284-324.) Used with permission

Hosseini and Gordijn go on to explain that the discussion of author attribution includes 2 discrete issues. The first is about recognizing both nonintellectual contributions (such as enrolling patients for clinical trials or providing writing assistance) and intellectual contributions (designing and conducting research, analyzing and reporting results, etc). The second issue within the attribution theme is the question of the amount of effort an individual must contribute in order to receive credit. The authors point out, for instance, that the notion of requiring "a significant or substantial contribution" as a prerequisite for authorship has triggered extensive discussions throughout the field.

Unfortunately, few if any of these thorny issues have simple or straightforward answers. Nevertheless, experts in many scholarly disciplines—and across the field of scholarly publishing broadly—provide guidance regarding who should and should not be listed as authors in academic works.

International Committee of Medical Journal Editors Guidelines

The International Committee of Medical Journal Editors (ICMJE) is perhaps the leading authority in the health sciences authorship landscape. According to its website, the editors of 14 journals are currently official members of the ICMJE, including those of *Annals of Internal Medicine*, *British Medical Journal*, *JAMA* (Journal of the American Medical Association), *New England Journal of Medicine*, and *The Lancet*. The ICMJE affirms the importance of properly assigning authorship: "Authorship confers credit and has important academic, social, and financial implications. Authorship also implies responsibility and accountability for published work."

In its recommendations entitled "Defining the Role of Authors and Contributors,"³ the ICMJE explains why authorship matters, defines who is an author, and provides guidance regarding the

treatment of nonauthor contributors. Importantly, the ICMJE has published standards for authorship that are widely recognized within healthcare publishing. The standards were first published more than 40 years ago “as a way of standardizing manuscript format and preparation across journals. Over the years, issues in publishing that went well beyond manuscript preparation arose, resulting in the development of separate statements, updates to the document, and its renaming to reflect its broader scope.”⁴

Today, hundreds of medical journals follow the ICMJE recommendations that authorship be based on 4 specific criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In many respects, these 4 criteria represent the bedrock guidance regarding the designation of authorship in health sciences publishing. To be clear, ICMJE suggests that “all those designated as authors should meet all 4 criteria for authorship, and all who meet the 4 criteria should be identified as authors.”

Beyond the ICMJE, other publishing associations offer largely parallel guidance regarding authorship in healthcare:

- The Committee on Publication Ethics (COPE) manages a multifaceted website dedicated to authorship,⁵ with resources including case studies, guidelines, flowcharts, discussion documents, seminars/webinars, and e-learning. As part of its contribution, COPE has also published an excellent discussion document entitled, “*Authorship*,” which highlights COPE’s focus on transparency regarding who has contributed to a work (and in what capacity) and describes processes for managing potential disputes.⁶ Among its other contributions, the COPE paper provides a list of author resources for negotiating authorship, determining the order of authorship, and contracting among authors.
- The Council of Science Editors (CSE), another important resource on issues in the communication of scientific information, fosters networking, education, discussion, and exchange within the scientific publishing community. CSE’s *White Paper on Promoting Integrity in Scientific Journal Publications* offers an in-depth analysis aimed at developing and improving effective practices (including authorship practices) that promote probity in scientific publishing.⁷

ISPOR Authorship Guidance

The health economics and outcomes research community has taken great care to provide clear direction regarding authorship. ISPOR encourages its members to adhere to fair and equitable

requirements for authorship and to respect their colleagues in the process. In its most recent Code of Ethics,⁸ ISPOR highlights these authorship themes:

The named authors formally take responsibility for the report of the research. Therefore, some study users view the identity of the authors as one indicator of the likely quality and reliability of the research, although when acting as editors or reviewers of papers for journals, ISPOR members should make judgments based solely on the quality of the research, not the identity or affiliations of the authors (if these are not already anonymized by the journal concerned).

Authorship also provides recognition of the researchers’ contribution. Therefore, it is wrong to include an author who did not make a substantive contribution due to their name recognition and perceived status. Similarly, it is wrong to exclude an individual who had made a substantial contribution because of their affiliation.

Furthermore, in the Instructions for Authors for ISPOR’s journals *Value in Health* and *Value in Health Regional Issues*, the instructions specifically note that the journals use the previously described 4-criteria guidance set forth by the ICMJE for defining the role of authors and contributors.⁹

Value in Health Commentary and Editorial Contributions

The current issue of *Value in Health* tackles the authorship question in 2 brief but informative pieces.

First, in his commentary titled “Let’s Make Sure We Are Doing Authorship Right,”¹⁰ Jaime Caro asks and answers 2 core questions that the guidelines do not address directly: (1) Are there acceptable grounds for excluding from authorship anyone who meets the 4 ICMJE criteria (or for including some who do not)? (2) What is the appropriate author order?

Caro argues that there are no acceptable grounds for excluding from authorship someone who qualifies. “If someone meets the criteria, they should be authors,” Caro says. He goes on to address several subsets of the core question, contending, for example, that “gift authorships” (granting undeserved authorship status to a well-known key opinion leader) “is clearly inappropriate, and the common practice of having the gift recipient briefly review the final manuscript does not qualify them for authorship.” Caro also touches briefly on the legal and moral conundrum of “work for hire,” offering suggestions to prospective authors meant to help support their claim to authorship.

Finally, Caro observes that the order in which authors are listed can be particularly contentious and “driven by criteria for promotion, appearance in citations, and the perception that order conveys the author’s role in the work.” In the HEOR field, the person listed first is generally considered the principal author and the one listed second is the next most responsible, he notes. Historically, says Caro, the last author listed was often “the head of the laboratory or department where the work was principally done, even if that person contributed insufficiently. This is inappropriate and constitutes a type of gift authorship, clearly discouraged by the ICMJE guidelines.”

In response to Dr Caro's commentary, the *Value in Health* Editors-in-Chief, Michael F. Drummond and C. Daniel Mullins, remind us in their editorial¹¹ that while authorship decisions are important in any setting, they are particularly so in academia because they can affect promotion and tenure. They go on to note that because journals rely on self-report, "there is always the possibility that the contribution of a given individual may be overstated. For this reason, *Value in Health*, in common with many other journals, insists that every author completes the ICMJE disclosure form personally."

Finally, Drs Drummond and Mullins point out that *Value in Health* recognizes the first author as the primary author unless the authors specify co-primary authors. Beyond that, there is no significance given to the subsequent order of authors, since some author groups list the coauthors alphabetically, whereas others may seek to list authors in order of contribution or seek to place the second most prominent author at the end of the list.

Conclusion

Taken together, the guidance described here can be largely reduced to a simple concept: all individuals who meet all 4 of the ICMJE specific authorship criteria—and only those individuals—should be listed as authors of a scholarly work. Finally, guidance regarding the order of authors is imprecise and each authorship group should carefully discuss and manage author order based on agreement within the group. •

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About the Author

Steve Crow is a board-certified editor in the life sciences with more than a decade of real-world healthcare writing and editing experience.

Balancing Liberty and the Common Good During a Health Crisis:

Two Behavioral Economists' Views of Citizen Reactions to COVID-19 in the United States

BY MICHELE CLEARY

Please stand
here to keep your
social distance

AS WE BEGIN JULY 2020, THE UNITED STATES CONTINUES TO battle rampant COVID-19 spread. While many countries within Asia and Western Europe have tamped down their COVID-19 hot spots, infections continue to roar across the United States with many states setting new case records daily.

Maricopa County, Arizona—home to Phoenix, the capital city of 4.5 million people—currently reports nearly 3000 new cases a day, eclipsing that of the boroughs of New York City, even on their worst days.^{1,2}

“This is not bad luck,” declared Arizona Public Health Association Executive Director, Will Humble. “The public policy that we developed and that was used at the end of the stay-at-home order really set in an honor system,” he said. “And an honor system isn’t adequate to direct the kind of human behavior that we need to slow down the spread of this virus.”³

This article examines how human behavior is complicating COVID-19 containment efforts (mask wearing, social distancing). Behavioral economists Kevin Volpp, MD, PhD, and Doug Hough, PhD, shared their perspectives on citizen choices to comply with COVID-19 mitigation and how culture leads to significantly different experiences during this pandemic.

Revelers and Revelations From the Lake of the Ozarks

In the United States, COVID-19’s early wrath targeted large metropolitan centers, especially New York City, while most states experienced only minimal infection rates. This inconsistent COVID-19 experience led many state leaders to disparage the economic costs that accompanied the COVID-19 shutdown. Eager to return their states to pre-COVID-19 operations, these leaders have supported a more casual approach to (if not full disregard of) virus control initiatives. Many of these states enthusiastically opened businesses and recreational sites as highlighted in the now infamous images of Lake of the Ozarks, Missouri, from May 2020.

Kevin Volpp, MD, PhD, Director of the Center for Health Incentives and Behavioral Economics at the University of Pennsylvania in Philadelphia, found these scenes upsetting, yet understandable. “I think that people tend to make decisions based on how they feel as opposed to any deliberate cognitive process,” said Volpp. “People aren’t very good at weighing future costs versus immediate gratification.”

Volpp continued, “I think what we’re seeing is that there are some subsets of the population who, when asked, are making a rational calculation—that the benefit of wearing a mask outweighs the downside, the risks, the costs. They will continue to socially distance pretty reliably. But a lot of the population won’t.”

He suspects that these Lake of the Ozarks partygoers view any potential harm from the virus as probabilistic, that it is in the future. “There’s no guarantee it will happen. And people are not very good at estimating probabilities to begin with.” Volpp added that the limited available data resulted in many viewing their risk to contract the virus to be largely intangible. “I think that all conspired to make it more likely that people would engage in risky behavior.”

Individuals’ Inability to Assess Risk

Douglas Hough, PhD, associate scientist at Johns Hopkins University in Baltimore, Maryland, agreed that many people are having an emotion-driven response to COVID-19 restrictions, fueled by the need for immediate gratification. “People are not calculating bodies,” he said. “They’re not doing cost-benefit analysis, looking at the discounted present value of future earnings. They’re just feeling that they’ve sacrificed. I’ve been at home for 8 weeks and nothing has happened.”

Hough noted that citizens often struggle with applying statistics to their own lives. “We’re asking people to assess their own risk for COVID-19 or other diseases.” In his view, people often view “low risk” as “no risk” despite someone usually being in the numerator. “They’ll just round up or round down to zero and say it’s practically zero,” he continued. “Do they do the math? No. Instead they think, ‘No, it’s not going to be me.’”

Variable Distribution of Risk

Hough identified the variable distribution of virus risk as reinforcing many people’s underassessment of their own risk. Until recently, COVID-19 cases were largely concentrated in a few geographic centers in the United States and globally. Even in these hot spots, those most severely affected were predominantly persons from older age cohorts (over age 65). Under these conditions, Hough argued that salience becomes very attenuated. People see their risk as minimal when no one in their social circle has experienced infection. “They say that they don’t work at a chicken processing plant, don’t know anybody who does,” stated Hough.

However, Hough continued that people need to understand that they do not necessarily need such proximity to be at risk. “You don’t have to know somebody who does. You just need to know someone who knows somebody who was in the store next to somebody whose family member works at the processing plant,” he said.

In Hough’s view, contact tracing could have different short- and long-term effects. “My sense is that when someone is informed that she has been in contact with someone who has been diagnosed with COVID-19, the salience of the disease will be heightened and behavior will be more circumscribed.” Hough warned of noncompliant behaviors if that person learns that her test comes back negative. “She will feel invincible (after all, she came close to the disease but did not succumb), moral hazard will take over, and she will begin to take more risks (less social distancing, less wearing of a face mask). A negative test result may be perceived as a ‘free pass’ from the disease.”

Taking Risks for Social Justice

Yet this year, risky social gatherings have not been limited to bars and beaches. While partygoers gathered in spots like Lake of the Ozarks, millions of protesters gathered in hundreds of towns and cities around the world to protest systemic racism and police brutality in response to the death of George Floyd in Minneapolis, Minnesota. While these protests did violate social distancing recommendations, Volpp saw the risk calculation somewhat differently.

“I think a lot of people weighing benefits and risks are deciding

they need to participate in these protests because it's a moment in history that hasn't come along very often to really try to change the system. And I think a lot of people feel a deep need to be part of that and to try to contribute to it. And that in essence weighs on the benefit side of the equation."

The Weight of Social Networks

Regardless of whether people are gathering to protest or to socialize, the individual decision-making calculus of social participation is heavily influenced by one's community. "People are very powerfully influenced by what others in their social networks do," Volpp said. "I think in both cases you have, for very different reasons, people influencing each other's actions in ways that make a certain course of action, much more likely than it otherwise might be."

"One of the challenges for us in this country has been to try to balance individual freedoms, which we hold so dear, with pandemic control."

Failing to Protect the Social Good

Volpp views noncompliance with social distancing and mask-wearing risks as rife with negative externalities—one's choice not to social distance or not to wear a mask imposes costs on others. He likened this behavior to that of chemical factories spewing soot in the air. "The chemical factories should have to cover the cost of that." In the same vein, in public health epidemic situations, we need to have stronger enforcement of actions that impose harm on others.

To achieve meaningful success over the virus, citizens must act together and comply with basic initiatives. The common good can result only from millions of conscious choices.

Echoes of de Tocqueville

To Hough, the need to protect the common good is echoed in Alexis de Tocqueville's *Democracy in America*. Said Hough, "We are very independent, yet we are perfectly willing to help our neighbor. Government, not so much, but our country, very much so." He continued, "This is part of who we are. I think it's definitely an American trait."

However, Volpp highlighted the inherent difficulties in this American approach when applied to public health. "One of the challenges for us in this country has been to try to balance individual freedoms, which we hold so dear, with pandemic control." He continued, "I think the pandemic is largely winning. As you see the number of cases continuing to shoot well past a hundred thousand in the United States with no sign of letting up, we haven't as a society really been able to figure out how to balance this."

The Ladder of Interventions

To change human behavior and bring US infection rates under control like other similar nations, Volpp proposed a ladder of behavioral intervention options. Options on the bottom would be gentle nudges, such as informing citizens that COVID is dangerous to their health. "That in itself probably doesn't accomplish very much, but it's also very nonintrusive."

Higher up the ladder would be more effective, but also more constraining approaches. "You can use some type of social norming intervention. You could think about positive incentives or rewards. You could think about penalties, financial penalties." At the top would be ways of changing choice architecture and defaults. "The most effective approach clearly, and you see this in terms of epidemic control in places like China, is to just eliminate choice altogether."

The Carrot or the Stick

Volpp shared his doubts that the United States has the appetite to enforce effective COVID-19 measures or penalize people who will not wear masks. "I'm not very optimistic about that. I feel like we're not going to be as successful at controlling the epidemic." He expects most Americans view heavy-handed measures to be "nonstarters." "In various parts of the country, we're trying to restrict choice by having people work from home where possible, but increasingly, I think the balance is shifting where this was more like an opt-out kind of default."

Regarding the workplace, Volpp stated, "I would say it's shifted from a restriction or elimination of choice where most workplaces required you to do it to now. I think increasingly, people get the option of going back to work and that's likely to make endemic control less effective. It's all a balancing act. We may go back and forth, you know, up and down this ladder, in essence, depending on how things go."

China, Volpp noted, has achieved some success by imposing highly restrictive measures. However, wide acceptance of less restrictive COVID-19 measures in China, such as mask wearing, may also stem from its recent experience with SARS.

For the United States, Volpp proposes a more targeted approach of restrictions. "I think this is a situation where sticks are much more effective than carrots. The vast majority of people will hopefully comply with what they're being asked to do. And so it makes more sense to penalize the relatively small proportion of people who are not complying than reward the vast majority of people who are complying. That would not be a very efficient use of resources."

Personalizing Infection Risks

Hough proposed adherence tools that personalize the disease and its risks—a mass customization of messaging. "Public health has demonstrated that you've got to make the case almost on a one-on-one basis. Finding ways of explaining to different kinds of people who have different pressures, different reasons, why they're not adherent, why they're not taking the drugs, why they're not getting vaccinated, and finding ways of identifying those people and getting the target."

He noted that this approach requires trusted spokespeople and emotional stories that people identify with as opposed to "just the numbers." He highlighted the *Washington Post's* ongoing stories of COVID-19 victims as an effective way to help people internalize this risk.

Hough also emphasized the value of trusted messengers to relay disease information—trust being a critical component of public compliance with COVID measures. "My sense is that

people are looking for somebody they can trust.” He pointed to Anthony Fauci, MD, director of the National Institute of Allergy and Infectious Diseases at the US National Institutes of Health, as an ideal spokesperson. “Here’s a guy who seems to shoot straight not just with data, but he seems to be telling the truth. He doesn’t seem to have an agenda. He seems to really do things in a solid way.”

Yet, Hough warned that the lack of general trust in government authorities—something that has grown in recent decades—makes such efforts challenging.

Preparing for Future COVID-19 Waves

Looking towards Fall 2020, both Volpp and Hough voiced concern about public exhaustion with COVID-19 measures as we face the likelihood of a worsening pandemic. Volpp lamented that the United States has been mired in a suboptimal situation for much longer than countries that have enacted more restrictive initiatives. He cited countries across Asia and Europe that have opened schools and businesses, where the rate of new cases is lower, while the United States has incurred an enormous human and economic toll. Volpp stated, “We’re paying very dearly for having a more hands-off response, leaving it to individual, state-level governments to figure this out without a lot of federal backing.”

Hough shared similar concerns. He also feared far lower adherence to infection control measures. “People are thinking, ‘Alright, I did my civic duty. I stayed home at that significant personal social cost and nothing happened to me or my family or to many people that I know of. And now you’re telling me to do it again? I don’t buy it.’”

“We’re paying very dearly for having a more hands-off response, leaving it individual, state-level governments to figure this out without a lot of federal backing.”

Public Reaction to Vaccination

As we look forward to a possible vaccine, Volpp anticipates people’s COVID-19 experiences resulting in 2 possible responses. “It would make people more conscious of the importance of their health, in disease, thereby making people more adherent to immunization recommendations.” He continued, “The other side of that coin is that a lot of conscientious people who would be getting those vaccines are also very apprehensive about leaving their homes and going to places where there might be a lot of other people. I’m worried that this fall, this winter, that vaccination rates might be much lower because people are reluctant to go to places where they’re worried that they could get exposed to the virus.”

COVID Compliance Today

Many state and federal leaders in the United States are now pressing for the reopening of businesses, schools, and services in hopes of reversing the COVID-related economic slowdown. But while many Americans are done with COVID, the virus is in no way done with them.

The rapid reopening has fueled an enormous surge in new

cases with 1 million new cases of the novel coronavirus in just the month of June. The growth in new cases is exceeding that seen this past spring. Parts of Texas, Arizona, California, and Florida are facing zero or minimal capacity in their critical care units.⁴

In Miami, Mayor Francis Suarez shared his concerns about individual compliance with social distancing and mask wearing. “I think the problem that we’re having is the behavior. When we allowed businesses to open, citizens just went out and pretended like this virus didn’t exist.”

Like many officials within COVID-19 hot spots, Mayor Suarez is struggling to compel citizens to comply with containment measures. The city recently required masks in public, fining those who fail to abide with increasing fines for each citation: first, a warning; the second time, a \$50 fine; third time, a \$150 fine; and finally, a \$500 fine.

“I think the biggest issue right now is making sure that we can address behavior and that our residents understand that we’re in this together,” Suarez stated. “If we don’t pull it together, we’re going to have major issues with our hospital capacity and we’re going to have major issues going forward.”

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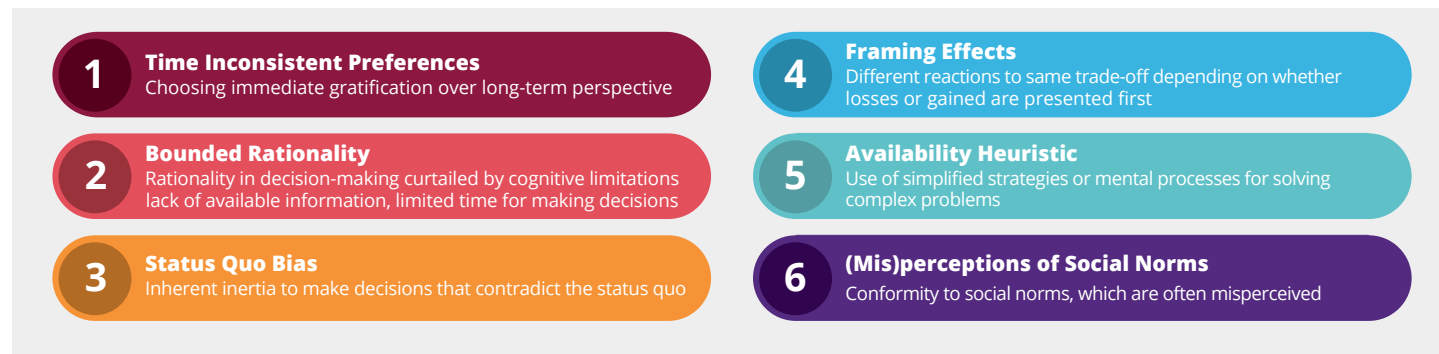
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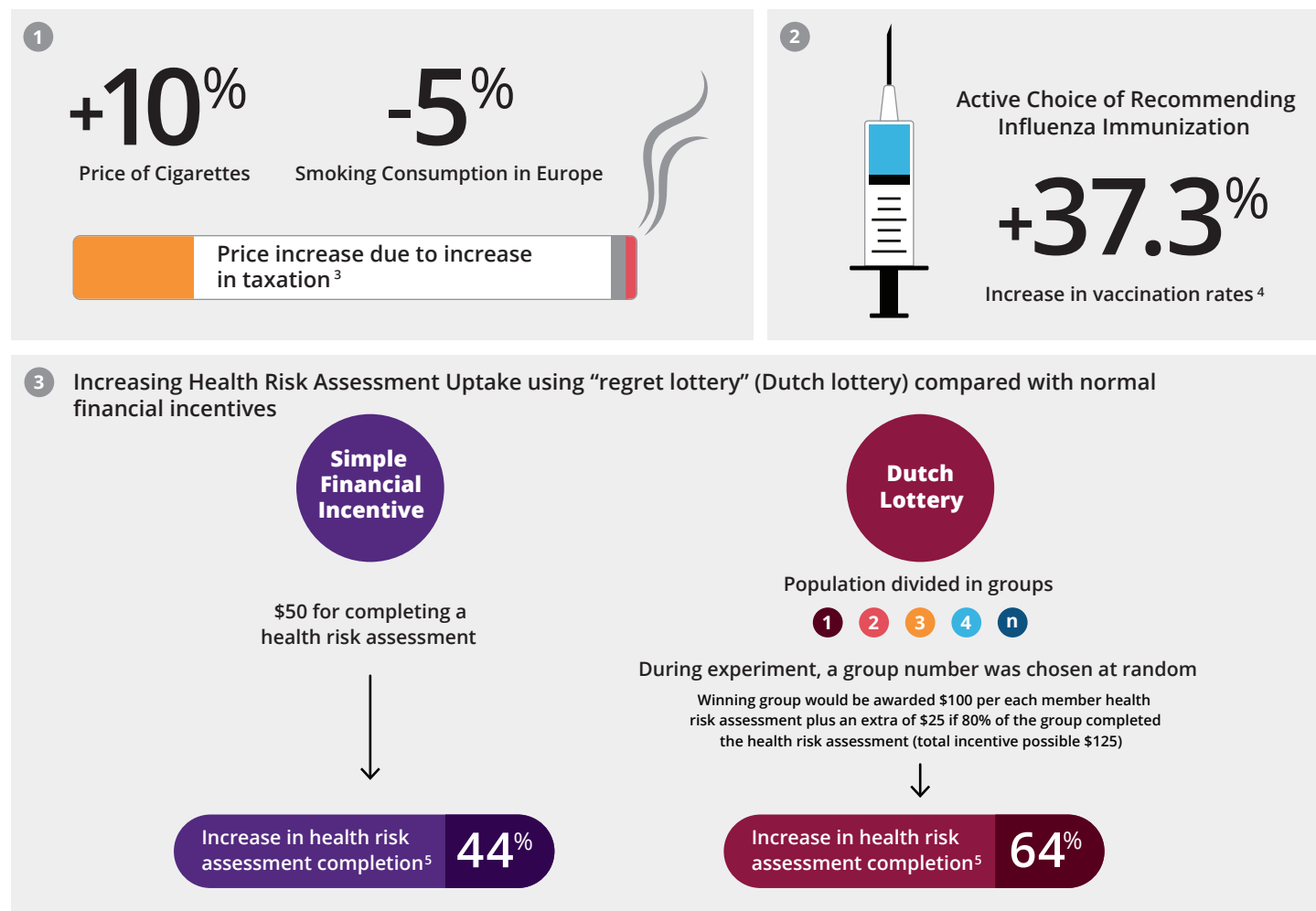
By the Numbers: Behavioral Economics

Section Editor: The ISPOR Student Network

6 COMMON BEHAVIORAL CONCEPTS FOR PUBLIC HEALTH POLICY ¹



SUCCESSFUL APPLICATIONS OF BEHAVIORAL ECONOMICS IN HEALTHCARE



Contributors: Aakash Bipin Gandhi, Chintal H. Shah, University of Maryland, Baltimore, MD, USA; Nazneen Fatima Shaikh, Mona Nili, West Virginia University, Morgantown, VA, USA; Krystal Williams, Florida Agricultural and Mechanical University, Tallahassee, FL, USA; Vasco Pontinha, Virginia Commonwealth University, Richmond, VA, USA

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Value-Based Pricing, Cost-Effectiveness Thresholds, and Affordability: Are They Compatible?

Patricia M. Danzon, PhD, The Wharton School, University of Pennsylvania, Philadelphia, PA, USA

We discuss alternative tools that can be used to reconcile cost-effectiveness analysis and value-based pricing with affordability, through a focus on 3 budget challenges: high-volume/high-price treatments, costly cures, and orphan drugs.

Cost-effectiveness analysis (CEA) and value-based pricing (VBP) are tools designed to enable payers to maximize health gain for enrollees, given the payer's budget/revenue constraints. Systematic application of CEA-VBP requires that the payer, as agent for its enrollees, defines rules for measuring the incremental cost-effectiveness (CE) of proposed new treatments, relative to current treatments, and sets a CE threshold (eg, \$150,000 per quality-adjusted life year [QALY]) that reflects its willingness to pay for health gain. To gain reimbursement approval, new therapies must be priced at or below this threshold, with possible exceptions for special factors. If payers adopt this CEA approach to reimbursement, manufacturers are incentivized to adopt VBP, that is, to price a new drug based on its incremental effectiveness, valued at the payer's CE threshold. Use of CEA-VBP by payers thus not only maximizes enrollees' health gain from the payer's budget, but also signals to investors that research and development is rewarded if it delivers incremental value for patients.¹

This CEA-VBP approach evaluates pricing/reimbursement decisions based on a drug's incremental value, without considering its budget impact. Ensuring affordability of all VBP treatments requires that, in the long run, a payer's budget and its CE threshold are simultaneously determined: the larger the budget, the higher the CE threshold can be, because a higher CE threshold implies reimbursement of more, higher-priced therapies. In the short run, the launch of new, abnormally high-price or

for new therapies and—implicitly or explicitly—adopt a lower CE threshold and VBP if expected budget impact is “too large.” This potentially discriminates against high-volume disease classes. An alternative approach is to lower the CE threshold across the board, eliminating reimbursement for previously marginal services. However, unstable reimbursement is potentially costly for providers and patients. Thus, although affordability requires that CE thresholds and budgets are interdependent in the long run, short-run adjustment of the CE threshold to manage affordability can be inefficient and inequitable.

This paper discusses alternative tools to reconcile CEA-VBP with affordability, focusing on 3 prototypical budget challenges: (1) high-volume/high-price treatments; (2) costly “cures,” such as gene therapies; and (3) orphan drugs.

1. High-prevalence/high-price diseases

This context arises for progressive diseases (eg, hepatitis C), which have increasing medical complications and costs over a patient's life. Highly effective new drugs that eliminate the underlying infection and avert high, late-stage disease costs can justify high, value-based prices. Importantly, for any slowly progressing disease, the stock (prevalence) of existing patients is large, relative to the annual flow (incidence) of new patients. If a payer provides treatment for all patients as soon as an effective new treatment becomes available, total initial treatment costs

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high-volume treatments can challenge affordability, that is, the payer's ability to pay for all VBP therapies that meet its CE threshold. This leads some payers to include “expected budget impact” in their coverage assessment

would be unaffordable within current budgets and far exceed future steady-state annual treatment costs. The short-term “budget bulge” occurs because (a) the projected cost-offsets that justify the high prices accrue mostly in future years,

for all early and middle-stage patients, and (b) the initial stock of patients potentially eligible for treatment far exceeds the annual flow of new patients.

Thus, high-volume/high-price challenges to affordability are greatest at the launch of highly effective treatments for slowly progressing, ultimately fatal diseases. In such contexts, immediate treatment is highly cost-effective for late-stage patients who face large, near-term medical and health costs. Immediate treatment is less cost-effective for early-stage patients with modest, near-term medical and health costs. In other words, progressive diseases imply both high patient prevalence and heterogeneity. Monitored treatment staging—treating later-stage patients immediately while deferring treatment of early-stage patients—can distribute the “budget bulge” across years and better align the incremental spending on new drugs with the accrual of cost offsets on other treatments, with minimal health risk for patients. Spreading treatment over time also allows time for entry of competing products that may offer expanded treatment options and lower prices.

Unsurprisingly, the most pressing affordability challenges have arisen from such highly effective new treatments for high-prevalence, progressive diseases, notably hepatitis C. Most payers managed the high-price/high-volume “budget bulge” by spreading treatment of the initial patient stock across years and by exploiting the entry of competitor products to negotiate price discounts. Going forward, the annual cost of treating new patients is more modest. The key to affordability thus lies in (a) recognizing that the initial “budget bulge” is temporary, because disease prevalence exceeds annual incidence; (b) understanding disease progression, to optimally manage treatment staging; and (c) creative contracting to exploit competitive entry and achieve lower prices.

2. High-priced “cures”

“Cures” are single treatments that promise lifetime reductions in medical costs and/or improvement in quality of life, such as gene therapy. The value-based price of such a treatment is potentially very high, because it reflects the present value of cost savings and QALYs gained over the patient’s expected life. Budget impact can thus be large for the initial payer who pays for treatment, while medical cost offsets and health gains are spread over the patient’s life and future payers. This misalignment of payment with benefits has prompted analogies with home mortgages and proposals for novel mechanisms that pay installments over time, possibly contingent on actual cost-savings and QALYs realized.

A major advantage of such pay-as-you-go mechanisms is that payment can be contingent on actual outcomes, to share risks as to long-term benefits of novel therapies and align producer incentives. Short-term, outcome-based contracts are increasingly being used by payers to appropriately tailor payments to outcomes realized. However, outcomes-contingent contracts entail monitoring and administrative costs, hence are most practical for treatments with readily observable outcomes in the short-term (eg, cholesterol reduction over 1 to 2 years). However, for long-duration “cures,” monitoring outcomes and attributing cause becomes increasingly problematic as time elapses. In practice, installment-payment proposals for “cures” ignore

key differences between medical care and home mortgages. Most medical care is covered by public or private insurance, and patients typically switch insurers over their lifetime, especially in the United States. The payer that agrees to administer and pay the first installment for a “cure” cannot legally commit future payers to make future payments. Granting such power would undermine the first payer’s incentive to be diligent in negotiating the total prices and fairly sharing payment with future payers, especially Medicare, which covers most patients after age 65. Future payers might litigate or default on their “liabilities,” with some justification if their formulary does not cover the treatment or if they incur unexpected treatment-related complications. Further, patients who carry with them a contractual liability for past treatment would likely encounter rejection and/or high premiums in private insurance markets, unless all health plans are subject to guaranteed issue/community rating requirements that mandate payment for prior treatment liabilities. From the producer’s perspective, if future payers default, no collateral/repossession remedy exists, analogous to repossessing a house if the buyer defaults on payment.

A major advantage of such pay-as-you-go mechanisms is that payment can be contingent on actual outcomes to share risks as to long-term benefits of novel therapies and align producer incentives.

In fact, gene therapies and other “cures” are not unique in offering long-term medical benefits. Arguments for installment payment could be applied to many existing drugs and medical services with long-lived benefits, including many surgeries, vaccines, and other long-lived treatments. Over time, any large payer pays for some long-lived treatments but benefits from others. Such diversification across patients undermines the affordability case for installment-based payments for long-lived treatments, although the risk-sharing and incentive alignment arguments for installment payments remain valid. However, the feasibility of measuring and attributing outcomes to treatments are key to making such contingent, value-based payment systems practical. Applying such contracts to long-term cures requires further research on outcomes measurement and attribution, and on the management of multi-insurer liabilities.

3. Orphan drugs

Rare diseases were traditionally of concern because they were neglected as unprofitable by R&D departments. This neglect led, in 1983, to the Orphan Drug Act (ODA), to incentivize R&D for rare indications, defined as less than 200,000 patients in the United States. The ODA provides special R&D tax credits and grants, user-fee waivers, and 7 years of market exclusivity. Although the ODA does not explicitly address pricing, higher prices for orphan drugs, both absolutely and per unit health gain (eg, price-per-QALY) have been rationalized on grounds that: (1) patient volume and hence budget impact is low for each orphan drug; and (2) high prices are needed to offset low volumes to cover fixed R&D costs and yield a competitive

return on investment. Although high prices are also sometimes rationalized by high “unmet medical need,” a lack of other effective treatments enhances the incremental value of an effective new treatment and hence would normally justify a high price within the standard CE threshold. Thus “unmet medical need” alone cannot support the use—implicit or explicit—of an abnormally high CE threshold for pricing any drug, orphan or nonorphan.

Since the ODA was enacted in 1983, the environments for orphan drug approval and reimbursement have changed dramatically. A recent study found that of the top 100 drugs in the United States, the average cost per patient/per year was \$140,443 for orphans versus \$27,756 for nonorphan drugs, with the highest-price orphan drug costing over \$500,000 per patient/per year. These large differences strongly suggest that orphan drugs receive a higher price-per-QALY than nonorphan drugs, on average, although unfortunately no systematic comparison exists of price-per-QALY for orphan versus nonorphan drugs.

The combined effects on R&D of the ODA incentives, easing of regulatory requirements through breakthrough status and high prices, have been dramatic. Since 1983, over 600 orphan indications have been approved² and orphan drugs now account for over one-third of new drugs approved by the US Food and Drug Administration (FDA) per year, with 30 to 50 new approvals annually since 2013. This surge in R&D targeting orphan drugs suggests that adding abnormally high pricing to the significant R&D incentives provided by the ODA and lower regulatory burdens, has made orphan indications more profitable than nonorphan indications, potentially biasing R&D towards orphan indications. Consistent with this, recent research found that phase III R&D cost was 50% lower for orphan conditions, and 75% lower after tax credits. Many orphan drugs are approved for multiple indications, including some nonorphan indications, and off-label use is common, such that patient treatment volume exceeds the orphan drug threshold for many orphan drugs. Overall, the expected return on investment was 1.14 times greater for orphan versus nonorphan drugs.³ Sales forecasts for pipeline orphan drugs now account for over a third of total R&D pipeline sales through to 2024.⁴ Thus orphan drugs in aggregate now pose an affordability concern for payers, and even individual, high-priced orphan drugs can have significant budget impact.

This growing share of new drugs and sales that target orphan conditions strongly suggests that pricing of orphan drugs using a higher CE threshold—implicit or explicit—is unnecessary to stimulate orphan R&D, given the statutory provisions of ODA (tax credits, market exclusivity, and fee forgiveness), supplemented by the FDA’s breakthrough status and other favorable regulatory provisions that apply to most orphan candidates.

This analysis suggests that payers should apply the same value-based pricing criteria and CE thresholds to orphan drugs as to nonorphan drugs. Those orphan drugs that provide highly effective treatments for unmet medical need will still qualify for high prices, while those that offer only modest benefit will receive a price that reflects their modest value. Pricing orphan

drugs using the standard CE threshold would reduce the orphan drug affordability challenge and provide more appropriate allocation of current health budgets and incentives for future R&D. Whether certain ultra-orphan conditions can justify special CE thresholds or other VBP considerations remains a subject for future research.

Conclusions

Although in the long run, payers who use VBP must consider their budgets in setting CEA thresholds to assure affordability, in the short run other tools can offer remedies that are better tailored to deal with specific affordability challenges. High-volume/high-price treatments for progressive diseases can be managed by staging treatment of the initial patient stock over several years, after which annual treatment costs are modest. High-priced “cures” may be amenable to short-term, outcomes-contingent payments, but long-term installment payment is problematic and unwarranted. Pricing orphan drugs using standard CE thresholds would eliminate the orphan drug affordability challenge for payers, while preserving ODA and FDA provisions that mitigate R&D costs for orphan drugs. •

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Opportunities and Challenges Incorporating Patient Preference Information in Health Technology Assessment Frameworks

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The main challenges related to the integration of patient preference information in health technology assessments are about the choice of method of analysis of patient preferences and the documentation of preference heterogeneity.

Today, integration of patient preference information (PPI) plays an essential role in the development and implementation of healthcare interventions and health technology assessment (HTA) decision making. The institutional incentives are aimed to strengthen patients' rights and encourage (potential) consumers to contribute directly to guideline developments and assessment of health technologies or programs.^{1,2} The use of multiple-criteria decision analysis to support healthcare decisions has increased debates about how to incorporate patient preferences into HTA decisions, such as by informing committee value judgments with evidence.³⁻⁵ However, there is no standard HTA approach that indicates how patient preferences should be included and elicited in healthcare decisions. Methods are emerging but seem to vary by stakeholder, country, or agency.^{6,7}

Why incorporate PPI in the HTA?

Incorporation of patient perspective is becoming essential at all the dimensions of decision making:

1. By consuming health technologies, patients not only gain benefits but also face adverse events/side effects. Therefore, insufficient knowledge about willingness to trade off perceived benefits versus risks might wrongly impact assessment of comparative-effectiveness and cost-effectiveness. Decision makers might not maximize patients' value.
2. Patients and professional healthcare practitioners might have different treatment preferences. Therefore, the democratic aspect and transparency of HTA recommendations require the integration of patient preferences in treatment guidelines and disease managements manuals. If not considered, patients might not accept treatments, resulting in poor treatment adherence/compliance in real-life practice.

3. Statements regarding comparative effectiveness and economic evaluation require aggregated unidimensional benefit scores or indices. Patient preferences can be used to estimate these utility or benefit metrics.

How can PPI be defined?

Decision makers have to adapt and incorporate PPI to support a paradigm shift towards patient-centered healthcare. The Institute of Medicine⁸ states that patient-centeredness aims at "providing care that is respectful of and responsive to individual patient preferences, needs, and values, and ensuring that patient values guide all clinical decisions." Therefore, the primary task of the regulatory processes is to assess outcomes and measures to reduce uncertainty and appraise that these outcomes are meaningful not only to clinical and policy decision makers, but also to patients. More specifically, the content of PPI has been defined by the US Food and Drug Administration (FDA) as "qualitative or quantitative assessments of the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions."⁹

How best to incorporate PPI in HTA frameworks?

HTA is expected to be an interdisciplinary process, which gathers scientific, contextual, and historical types of evidence. Depending on the aim, quantitative and qualitative methods are or can be used in HTA. Patients ask for more participation in the HTA process to gain representation and to make better informed decisions. The desire to participate in the decision-making process results from a perceived lack of recognition by patients. Therefore, the consideration of PPI in the process of HTA is required.

Three crucial questions help to understand how patient preferences can be recognized in HTA frameworks:

1. What matters to patients? What decision criteria are maximizing treatment benefits?
2. How can outcomes and endpoints be weighted? How can evidence about the maximum acceptable risk be documented?
3. How can the net benefit be assessed related to the decision-relevant outcomes? What is the best way to aggregate effectiveness measures and assess heterogeneity and uncertainty surrounding these outcomes?

The first question covers the procedural dimension of PPI. The next 2 questions are together related to the methodological aspects related to the use of PPI in HTA.

Integration of patient preferences in chronic diseases (ie, rheumatoid arthritis) is a good example that answers these 3 questions and shows how patient preferences for rheumatoid arthritis with biologic disease-modifying anti-rheumatic drugs (DMARDs) might support HTA decision making.^{10,11} First, patients' preferences contribute to inform decision makers on the patient-relevant decision criteria of DMARDs therapeutic classes (eg, route of administration, effectiveness, treatment-specific rare risks).

Second, elicitation of relative importance can be estimated using discrete choice experiments, which can be administrated to a representative sample of the population of interest.^{12,13} Health preference research can provide information on patients' willingness to trade off benefits versus risks. Third, to support the related effectiveness or cost-effectiveness healthcare decision, the patients' weights might be combined with those of other HTA stakeholders through a consistent, a transparent value assessment framework. The latter process should be optimized by analyzing the impact of the preference heterogeneity (identified by specific subgroups) on the outcome measures of the healthcare decision (eg, remission) or cost-effectiveness metrics (eg, incremental cost-utility ratio).

What are the key challenges related to the use of PPI in HTA and economic evaluation?

The main challenges related to the integration of PPI in HTA are mainly procedural and methodological. According to a recent systematic review,¹⁴ the most methodological issues are about the choice of method of analysis of patients' preferences (narrative approach or patient's elicitation) and the documentation of preference heterogeneity. A controversial question frequently discussed by HTA decision makers is how to use PPI beyond the quality of life-years given that patient preferences capture the differences in health states experienced by patients.⁷ In that regard, an example illustrating this issue is how HTA decision makers use PPI related to the patient preferences for rheumatoid arthritis with biologic DMARD.¹³

Conclusion

Despite conceptual progress in terms of the definition of PPI and the identification of its benefits in the HTA process, there is a lack of standard guidelines and a need for examples illustrating the impact of PPI on HTA decision making.

The crucial challenge is how to integrate PPI into value assessment frameworks using systematic and standard scientific approaches. Further research has to demonstrate how PPI can be incorporated into the existing guidelines and HTA value frameworks (eg, clinical, ethical, and economic HTA procedure) and the extent to which PPI can be considered as based evidence data. •

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PROactive—Linking Design, Analysis, and Interpretation of Patient-Reported Outcomes in Clinical Trials

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A good patient-reported outcomes strategy requires specificity, planning, and forethought. Linking PRO endpoints, analysis, and potential interpretations from the start helps make the most of patient insights collected from PROs within the trial.

Designing Meaningful PRO Endpoints

In designing patient-reported outcomes (PRO) endpoints, the first step is to think about how patients' symptoms and functioning will likely be affected by the drug (Figure). Next, it is important to speak to patients to understand which of these changes will be most impactful. Instrument selection should not necessarily be based on what similar trials have used, but instead on which instrument provides the best insight into the key domains of interest.

PRO endpoints should have a clear specification of what will be measured, how it will be measured, and what clinically relevant change looks like, as well as a prespecified hierarchy of PRO endpoints. It is unlikely that PRO endpoints supporting efficacy will be included in the US Prescribing Information unless they are included in the statistical hierarchy with a specific hypothesis. Spending type I error is not a decision taken lightly, so possible PRO endpoints need to be considered carefully. For example, prospective efforts should be made to guarantee appropriate data collection for an interpretable data analysis. For studies with regulatory intent, frequent communication with regulatory authorities is encouraged to help ensure the design and analysis plan will answer the research objective and adequately characterize the PRO endpoints of interest. In addition to efficacy, there may be instances where PROs provide complementary descriptive information about tolerability, as was the case with crizotinib for lung cancer (ocular toxicities).

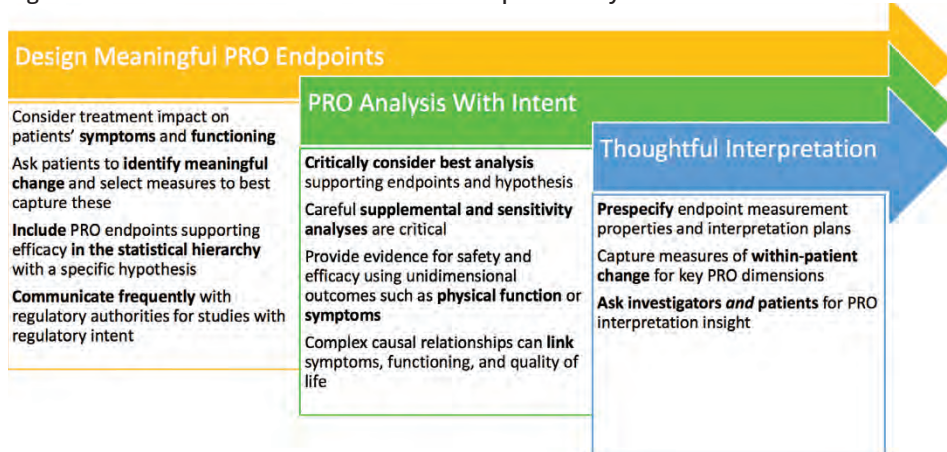
PRO Analysis With Intent

When designing the analysis plan, it is important to critically consider which analysis is best suited to the endpoints and the hypothesis of interest. Furthermore, analytic challenges that may result from trial design or

clinical context, such as asymmetric missing data or dropout, knowledge of treatment assignment, or frequency of assessment need to be considered at the design phase. Including careful supplemental and sensitivity analyses to address potential biases or concerns and demonstrate the robustness of the analysis is likewise important. Prevention is key but planning for possible contingencies arising from these issues (such as missing assessments due to unexpected intercurrent events) is not a waste of time. Different therapeutic contexts may require different analyses and endpoints, highlighting the importance of good design and early communication with patients to understand what you will be analyzing.

A common challenge in the analysis of PRO data from clinical trials is the use of the broad, multidimensional outcomes such as health-related quality of life as endpoints. Providing evidence for safety and efficacy is more straightforward if unidimensional outcomes such as physical function or symptoms are used. With multidimensional outcomes such as health-related quality of life, analysts should consider the complexity of relationships among its different aspects. Recent research shows that some symptoms affect other symptoms, which in turn affect patient functioning, which affects patient quality of life.¹ Thinking about the logical causal flow of relationships from the symptom to quality of life would likely suggest that it is a more complex relationship. For example, nausea likely affects vomiting, and both will result in increased fatigue, which will result in reduced physical functioning, which will lead to poorer quality of life. More complex analytic approaches may be required to evaluate multidimensional constructs such as health-related quality of life, and well-defined unidimensional outcomes will be more useful when thinking about efficacy.

Figure. Inclusion of PRO data in HTA submission per country.



Thoughtful Interpretation

As part of the analysis plan, measurement properties of the endpoints and a plan for the interpretation of the estimation of effect should be prespecified. To ensure meaningful interpretation, the outcome of interest should capture measures within patient change, if possible. This includes consideration of the indirect relationships among key dimensions of PROs and how to anticipate and interpret these results. In addition, careful attention should be paid to design elements, such as open-label design, that may affect interpretation of the results. Concerns have been expressed that patient knowledge of treatment assignment may affect their willingness to stay on trial, complete PRO measures, or impact their responses to the measures. Simple comparisons by treatment may be insufficient and require additional supplementary analyses to support interpretation.

Furthermore, identifying a clinically meaningful change is important. A highly recommended approach is anchor-based methods to investigate meaningful change thresholds, particularly when clinically meaningful change hasn't been already established in the population. Anchor-based methods require an explicit definition of minimal importance by defining the anchor. This may be supplemented with descriptive representations such as the cumulative distribution function and probability density function or kernel density plot curves to derive the thresholds for meaningful change as a data-driven approach.

Once results are available, both investigators and patients can provide invaluable insight into the interpretation of PRO data. The key is to present the results simply and clearly so they can be easily understood. By following these simple steps, it is possible to have PRO results from clinical trials that communicate meaningful findings to regulators, payers, physicians, and most importantly, patients. •

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Q&A

SHIFTING BEHAVIOR TO FLATTEN THE CURVE

Interview with Thomas Rice, Professor, UCLA Fielding School of Public Health

Thomas Rice, PhD is a distinguished professor of the Department of Health Policy and Management at the UCLA Fielding School of Public Health in Los Angeles, California.

Dr Rice has conducted research projects and published studies examining physicians' economic behavior, health insurance for the elderly, healthcare cost containment, and the role of competition in healthcare reform. He is a coeditor of the book, *Behavioral Economics and Healthy Behaviors: Key Concepts and Current Research*, published in 2017.



“I will say that regulatory tools are likely far more effective than behavioral ones and our leaders need to have the political will to enforce tough regulations particularly as future hot spots arise.”

VOS: People tend to prefer more immediate gratification, even at the expense of their long-term well-being during the COVID-19 pandemic. Why do you think people have reacted so fervently to the purchase of sundry items from stores and pharmacies, but have yet to embrace social distancing, hand washing, and the use of personal protective equipment?

Rice: Two reasons come to mind. The first is behavioral. People are keen to do things that are easy in hopes that this will fix their problems, an example of optimism bias. It's easy (if items are in stock) to purchase things, but it's much harder to both start and then sustain changes in personal behaviors such as hand washing, mask wearing, and social distancing.

The second is political. Purchasing things gives individuals choice on how they behave. But requirements about social distancing and mask wearing bump up against viewpoints on personal freedom versus the collective good.

VOS: Are the risks and benefits to the general public not clear (misperceiving new social norms)?

Rice: The risks and benefits are not as clear as they should be because of mixed messages mainly from government, but also from health professionals. Beginning with government, we have the example of the US President downplaying the pandemic all along and claiming we are on the verge of solving it. That provides enough fodder for people to go back to their old behaviors, a kind of status quo bias, I suppose. Different governors and mayors have given very different messages.

On the health professional side, first we were told not to wear masks, but now we're told it's essential to do so. We are told we can't open up, but then that we can even though we are in no better position than before vis-à-vis herd immunity, vaccines, or treatments. I'll give a personal example: my wife and I belong to the same medical group. In anticipation of an upcoming trip, we asked our respective doctors if we should get a COVID test. One said yes, the other, no.

Having said that, I think the risks and benefits are clear to a majority of the population, but as I said earlier, behavioral change is hard. It's easier to look at the data out there and use whatever justifies your own behavior, an example of confirmation bias but also, more generally, cognitive dissonance.

VOS: Later this year or early in 2021, we expect to see vaccines or therapeutic interventions for COVID-19. What does behavioral economics tell us about patient decision making concerning the use of vaccines and therapeutic interventions? Is there anything we need to consider now to ensure appropriate uptake in advance of their availability?

Rice: I don't think I'd look to behavioral economics so much as classic rationality: people are going to be incredibly anxious to get a vaccine and try to be first in line to do so. (I do worry whether, as a result, the first vaccines will be as effective as later ones might be.) This will look much the same as the run on toilet paper, but on steroids.

There's not much we can do about anti-vaxxers, but hopefully they are only putting themselves at risk (that's not clear yet, however). To me, the problems are not behavioral—they are production! I am pleased to see that officials and industry are thinking about—and putting a lot of resources into—how to mass produce a vaccine.

VOS: People are often bound by inertia. A great deal of research has gone into understanding “nudges” over the past decade and their ability to shift behavior. What behavioral “nudges” do you feel will need to be present to shift people's perspective to embrace social distancing, guidelines, personal protective equipment and other means to avoid contracting the virus?

Rice: That's a really good question. I think one of the problems is that the people who are most susceptible to getting COVID-19 and having severe health results are often not in a position to protect themselves. The 2 greatest hot spots are prisons and nursing homes; in both cases, individual behaviors cannot overcome the overwhelming environmental hazards. More

generally, lower-income populations often cannot distance at home and in their community and are often required to put themselves in harm's way through their work.

Here, behavioral economics tools are useful perhaps only at the margins, but they are potentially important: the people crowding bars and beaches usually are not those who face the above challenges. A good example is what we are already seeing in front of and inside shops: taping X's on the ground to show people where they can safely stand. Take advantage of availability bias by having sanitizing dispensers everywhere. The more public officials wear masks in public, the more likely the public will follow suit—a bandwagon effect. However, I do think regulations are more effective than behavioral interventions here. Every tool can help!

VOS: What does behavioral economics tell us about how healthcare systems have and are preparing for the COVID-19 pandemic moving forward?

Rice: I think behavioral economic tools will work only at the margin—at least in the United States, where the population has shown an unusual degree of present bias compared to other high-income countries. I have mentioned bandwagon effects and availability bias as ways to improve behavior. I am disappointed,

I think behavioral economic tools will work only at the margin—at least in the United States, where the population has shown an unusual degree of present bias compared to other high-income countries.

however, about how appeals to the health of others are falling on deaf ears. Young people hear repeatedly that by congregating they are putting their elders at risk, but it is having scant impact on behavior. I will say again that regulatory tools are likely far more effective than behavioral ones and our leaders need to have the political will to enforce tough regulations particularly as future hot spots arise.

VOS: As we conduct this interview, we are starting to see a wave of new cases of COVID-19 being confirmed across the country. Previously, health systems became overwhelmed by shortages and decision fatigue with respect to patient care. Does “loss aversion” help explain what might have been happening early in the pandemic with respect to decision making? Are there things we can learn and implement during spikes in case reporting and hospitalizations as we move forward?

Rice: I assume that you mean that people were behaving more responsibly then than they are now. I suppose that loss aversion could explain that—attributing a great deal of disutility to what could happen if you got COVID. But people have gotten inured; perhaps they have not encountered many cases, or maybe because most of the deaths are among old people.

Regarding what we can implement going forward, I think you need to distinguish between regulation and incentives. The strongest tools we have are not economic so much as regulatory. Close down business in hot spots. Prohibit congregating. And so on.

One set of estimates claims that if we did not do these things initially, rather than having 2 million cases, we would have had 60 million by now. These regulations are much more effective than trying to use behavioral tools, which in most cases help at most at the margins. •

Martin Marciniak, PhD, Vice President, US Medical Affairs, GlaxoSmithKline, Research Triangle Park, NC, USA, is the Section Editor for the Q&A column.

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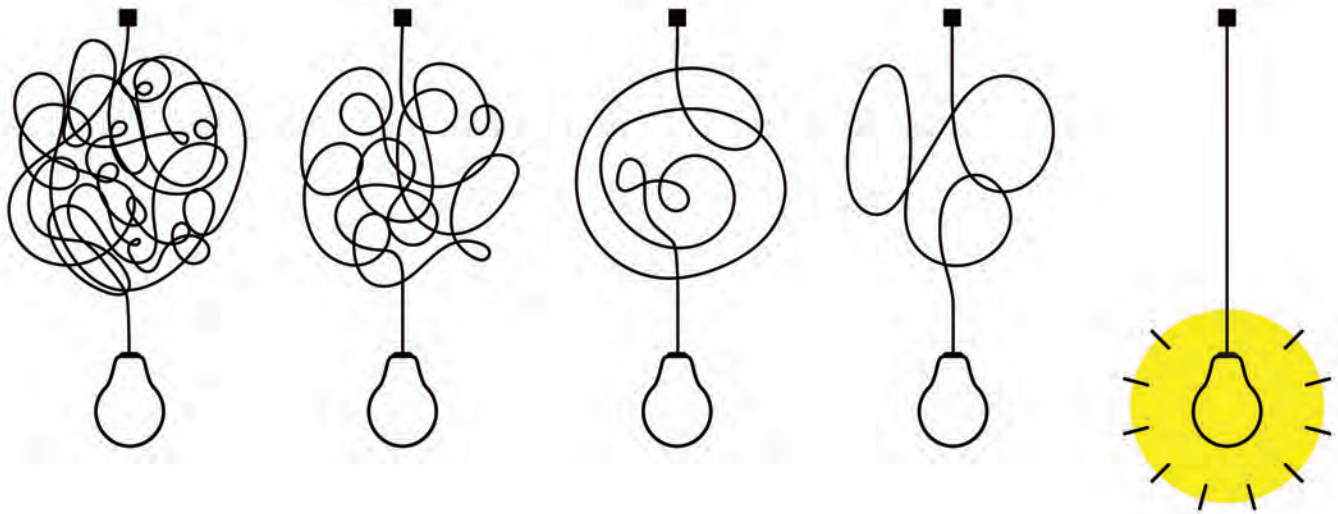


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