SEPTEMBER/OCTOBER 2018 VOL. 4, NO. 5

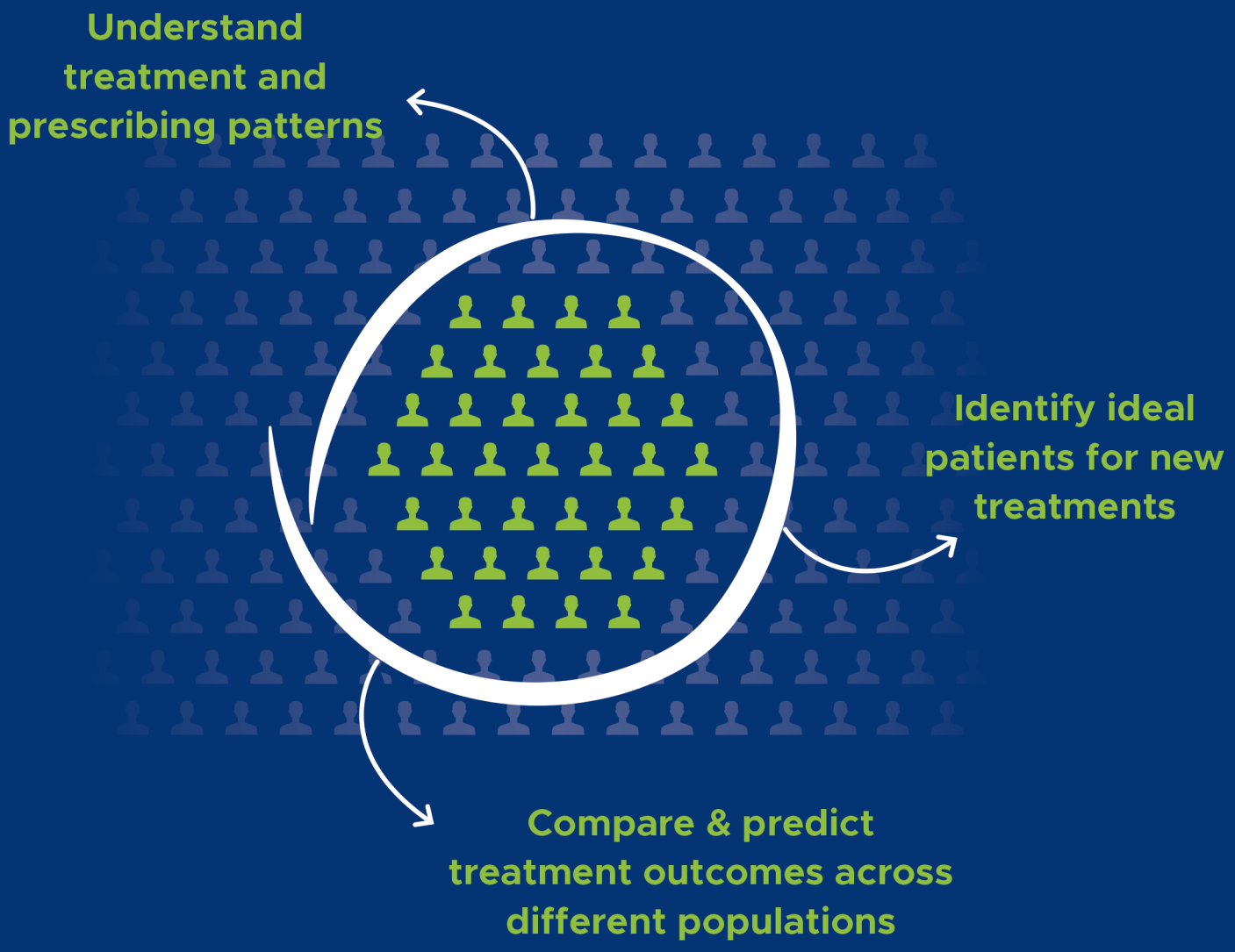
# VALUE & OUTCOMES SPOTLIGHT

*An ISPOR publication for the global HEOR community*

## How mHealth Technology Is REVOLUTIONIZING Clinical Research


IN THIS ISSUE:

# What if you could use curated registries to rapidly:

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VALUE & OUTCOMES
SPOTLIGHT

SEPTEMBER/OCTOBER 2018
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The mission of *Value & Outcomes Spotlight* is to foster dialogue within the global health economics and outcomes research (HEOR) community by reviewing the impact of HEOR methodologies on health policy and healthcare delivery to ultimately improve decision making for health globally.

ISPOR
*Improving healthcare decisions*

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## FROM THE EDITOR

Mobile Health initiatives, commonly captured under the abbreviated term "mHealth," center around the use of connected devices as a means of patient contact with the medical-care system. These devices include the common smart phone and other consumer wireless products as well as customized patient monitoring devices. All have in common functionality that leverages one or more wireless electronic communications channels, such as SMS text, 3G/4G telecommunications, GPS, and Bluetooth.

In general, mHealth can be considered an alternative—or, preferably, a supplement—to traditional forms of patient engagement, including physician office visits, telephone reminders, and ground-based ("snail") mail. The majority of innovations in this area relate to improving patient care and increasing efficiency in the provision of healthcare services. But mHealth also portends a revolution of sorts in the conduct of clinical research, particularly for the collection of real-world data.

Putting connected devices in the hands of patients—or tapping into their smart phones via so-called "bring your own device" (BYOD) approaches—represents an important advance in real-world research. It facilitates data capture from a broader swath of the patient population than could typically be enrolled into a registry-type prospective observational study, and it obviates the need for patients to come into clinics or study sites for assessments. Indeed, there are even initiatives to perform fully virtual studies in which there are no actual study sites.

mHealth also is completely simpatico with the concept of patient centricity, creating new challenges and opportunities for the measurement of study endpoints that matter to patients, and spawning new innovations in data capture. For example, while traditional PRO instrument instructions can be cumbersome to view on a smartphone screen, new technologies such as chat bots that guide the respondent through the questionnaire can be utilized.

This issue of *Value & Outcomes Spotlight* contains a feature article on the role of mHealth technologies in clinical research and, beyond that, a wide variety of articles of interest, including value assessment frameworks in oncology, estimands in health technology assessment, and health state utilities in cost-effectiveness analysis. Our ISPOR Central section reports progress on execution of our Society's IT strategic plan, which has already resulted in a revamped website, as well as an overview of the upcoming ISPOR Europe 2018 meeting in Barcelona.

See you there!

David Thompson, PhD
Editor-in-Chief,
*Value & Outcomes Spotlight*

## ISPOR SPEAKS

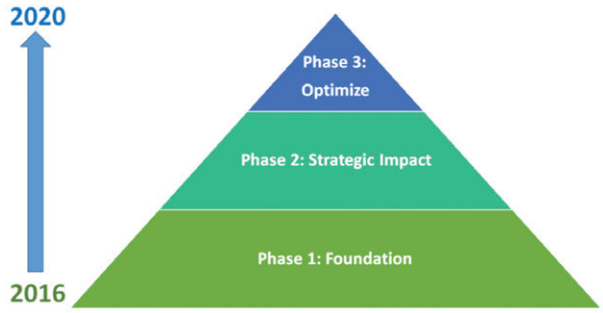
# Investments in Technology to Improve Services to our Members

**Sue Capon**, Chief Operations Officer

Over the past 23 years ISPOR has grown from a small group of founding members in the United States to the leading global professional association for health economics and outcomes research (HEOR) with more than 20,000 members in 110+ countries. As the Society's membership has increased and interest in HEOR has grown dramatically, we need to invest in our infrastructure to support current and future growth. Enhancing ISPOR's infrastructure is necessary as it impacts virtually every area of the organization—from staff development to governance and financial systems to information technology (IT). In many areas, the Society was lagging behind other associations of similar size and structure.

It was no surprise that a strategic review of our IT systems indicated a critical need for upgrading and updating our legacy systems. A 4-year IT strategic plan was developed with an ambitious timeline of multiple software implementations, network management changes, and staffing plans. Recognizing the need for our infrastructure to keep pace with our strategic plans, the ISPOR Board of Directors approved the IT plan and the corresponding investments of over US $1.25 million.

**ISPOR's IT Strategic Plan**




**GUIDING PRINCIPLES:**

- Support and align with the ISPOR organizational strategic plan
- Provide an exceptional digital user experience (members, stakeholders, staff)
- Promote a digital organization culture change
- Partner with expert service providers
- Improve technology through an ongoing, iterative process
- Implement a "cloud first" approach

**PLAN GOALS:**

- Establish a reliable and secure infrastructure
- Empower and enable members, other stakeholders, and staff
- Optimize and focus resources
- Become a data-driven organization

### PROGRESS ON THE IT PLAN

Significant progress has been achieved on the plan including critical network management changes and implementation of a new financial management system. At the end of July 2018, we simultaneously launched phase 1 of a new association management system (the equivalent of customer relationship management software) and a completely redesigned website powered by a leading-edge content management system.

Please visit our new and improved website that is optimized for mobile devices, offers enhanced navigation, and provides a powerful search engine. Joining and getting involved are much easier—see the Get Involved navigation at the top of the home page. Access to *Value in Health* and *Value in Health Regional Issues*, among our most popular resources, are now fully searchable. A new resource, Health Technology Assessment Central, is a comprehensive repository of resources and tools to support health technology assessment (HTA). HTA Central helps bridge the gap between HEOR and other disciplines that inform HTA and healthcare decisions.

The website is integrated with our new association management system—a technology platform that provides members with many benefits, including the ability to manage their member profiles, set communication preferences, and indicate areas of interest. >

We greatly appreciate the input from the global, multi-stakeholder IT Advisors Group of ISPOR volunteer leaders who served as a focus group for the project, providing feedback on navigation and scientific taxonomies.

**WHAT'S NEXT?**

Phase 2 projects are underway and will continue to streamline and improve our association management system and website. Projects include further website refinements and search optimization, as well as improvement of some longstanding website resources, such as the scientific presentations database—making these resources mobile friendly, aligning with our new taxonomy, and improving their functionality.

With these newly launched systems, we also lay the foundation for the future introduction of online collaboration tools. These tools will improve the ability for members to interact with each other by interest and/or regional areas.

Look for more changes to come that are designed to better serve you—our members—and the global HEOR community. For any questions or contributions to the initiative, please contact us at IT@ispor.org.

## Update Your Profile to Customize Your ISPOR Experience!

- Visit the new, redesigned ISPOR website at www.ispor.org
- Click the green "Log in" button in the top right corner
- Enter your email address and ISPOR Member ID# as password
- You will be requested to change your password
- Please use 'Forgot Your Password' to reset if you do not know your Member ID

*And remember to customize your communications preferences to receive only the emails that you want from ISPOR.*

In "My Full Profile," click on the "My Communication Preferences" link in the "My Account Links" box on the right-side of the webpage.

ISPOR AWARDS

# F. Reed Johnson: When it Comes to Health Economics, He's In It for Life

Don't expect F. Reed Johnson, PhD, ISPOR's 2018 Avedis Donabedian Outcomes Research Lifetime Achievement Award winner—a professor of medicine and in Population Health Sciences at Duke University, and a Duke senior research scholar, Duke Clinical Research Institute (DCRI) Preference Evaluation Research—to be retiring anytime soon.

"I tell everyone that they'll have to take me out feet first," jokes Dr. Johnson, a professor in Population Health Sciences at Duke University and a Duke senior research scholar, Duke Clinical Research Institute Preference Evaluation Research. "My friends keep asking me why I haven't I retired and I say I don't have a lot of outside interests. I have no interest in playing golf, for example. I like what I'm doing."

From Environmental Health Economics to Human Health

Dr. Johnson has more than 40 years of academic and research experience in health and environmental economics. As a staff member in the US Environmental Protection Agency's (EPA) environmental economics research program during the 1980s, he helped pioneer development of nonmarket valuation techniques. These methods are now widely used in federally mandated regulatory impact studies, for estimating the value of improved health outcomes, and for quantifying patients' tolerance for treatment-related risks.

He has more than 140 publications in books and peer-reviewed journals. He led the first US Food and Drug Administration's (FDA) sponsored study to quantify patients' willingness to accept benefit-risk tradeoffs for new health technologies. The study was used to inform recent FDA guidance on submitting patient-preference data to support regulatory reviews of medical devices. He has coauthored a book on techniques for using existing environmental and health value estimates for policy analysis. He is a founding member of the International Academy of Health Preference Research. He currently serves on the editorial board for The Patient, the Science Advisory Board for the EPA, and is an active participant on the ISPOR Health Science Policy Council.

"I think it's rather puzzling to people that I showed up [in the healthcare field] late in my career," Dr. Johnson told Value & Outcomes Spotlight. "I was an environmental economist for the first half of my career. It turns out that one of the largest benefit categories of reducing pollution is health."

He recalls that the challenge back in the 1980s was trying to do cost-benefit analysis for environmental services for which there are no markets.

"There's nobody buying and selling clean air or clean water," Dr. Johnson says. "During the Reagan Administration, they were requiring the EPA do benefit/cost analysis on all major regulations,

and we had no good way really of coming up with a monetary estimate of the value of reducing air and water pollution. The government made resources available to us, and to environmental economists in general, to start trying to figure out how to value what we called 'non-market goods' or nonmarket valuation. We developed some stated preference methods that eventually became widely accepted and are now just standard practice in government regulatory impact statements."

Eventually, Dr. Johnson found himself doing more studies about health and fewer about the environment, and ended up at Research Triangle Institute, now RTI International, conducting studies in health economics.

"When I started doing work in health, I kind of thought I was going to do the same thing," he says. "I knew there was reluctance to monetize health benefits, but if you are going to compare benefits with cost, you're going to need a monetary value, which is the same problem we had in environmental economics. As it turns out, though I thought we'd just fight that fight and win it again, it turned out to be a lot harder to persuade people that we ought to attach prices to outcomes. So, we continued to transfer the methods we used in environmental economics to health, but not so much for monetizing benefits but just to understand the relative importance >

## ISPOR AWARDS

of benefits and harms of new treatment. That's what we did for quite a long time and still are doing."

### THE COLLEAGUES WHO HAVE HELPED ALONG THE WAY

In the '90s, Dr. Johnson left RTI with some other colleagues to work in their consulting firm. But he was later persuaded to come back to RTI by Josephine Mauskopf, PhD, vice president, Health Economics Solutions.

In addition to Dr. Mauskopf, Dr. Johnson says there are others who have helped him achieve professional success. These colleagues include Brett Hauber, PhD, senior economist and VP, Health Preference Assessment, at RTI, who Dr. Johnson has worked closely with for more than a decade; John F.P. Bridges, PhD, at Health Solutions at RTI; and more recently, Shelby Reed, PhD, former president of ISPOR and professor in Population Health Sciences at Duke University; Deborah Marshall, PhD, MHSA, Canada Research Chair, Health Services and Systems Research; associate professor, Department of Community Health Sciences, Faculty of Medicine, University of Calgary; and director, Health Technology Assessment, Alberta Bone and Joint Health Institute, Calgary, who also is a past president of ISPOR; and Dr. Ben Craig, who has founded a new professional organization for stated preference research in health, the International Academy of Health Preference Research (IAHPR).

Dr. Johnson is also a member of in the Duke Clinical Research Institute. "Shelby managed to find a place for me at Duke 4 or 5 years ago, and we've managed to attract a few of my former colleagues from RTI and are doing much the same thing that I've been doing all my career," Dr. Johnson says.

"All of these people, I have to say, have made it possible for me to do what I'm better at," Dr. Johnson says. "And what I'm not better at is all of the, I guess you could call it, watering and weeding that has to go on in any sort of research activity. We must function in a complicated institutional framework, and I'm not very good with dealing with bureaucracies and making things happen. And so, I've been lucky in that people like Brett and Shelby are willing to clear the way for me, so I could do what I'm better at, while they dealt with a lot of the management aspects of our research. It's really, really important, and I couldn't have done anything that I've been able to do without them."

### LOOKING TOWARD THE FUTURE

Dr. Johnson says while stated preference research and its methods have come a long way, there is still much more progress to be made.

He points out that there are some barriers to the establishment of stated preference data as a routine element in both regulatory decision making and drug and device product development. "There is maybe a little bit of mistrust in patients' ability to think clearly and logically about the tradeoffs that are involved in healthcare," Dr. Johnson says. "It's hard for clinicians to see stated preference data as data in the same sense as trial data are viewed. And one of the primary goals of our research has been to make these studies, as much as possible, look like the kinds of controlled data collection efforts that are the basis of events-based decision making in health. I think we've made some progress in establishing some standards for doing these kinds of studies, in establishing validity tests that establish whether the data we have could stand up to the standard expectations about evidence. But it's hard to do this well—it's hard to do it at all. There aren't the resources available that are obviously available for other kinds of data collection in health."

According to Dr. Johnson, he was "honestly surprised" to be selected for the ISPOR Avedis Donabedian Award. "I felt in some ways that we weren't ready for that kind of recognition," he says. "But we have in fact made quite a bit of progress in the last few years, which has been gratifying."

This progress is reflected in the growing popularity of stated preference method topics for ISPOR's conferences. "It feels different than it did for many years when it was hard to get on the ISPOR program," Dr. Johnson says. "It's not so hard anymore, there seem to be a lot of people who are signing up for the conference courses and attending sessions. But still, I see a surprising—well, I guess surprising to me, considering how much attention stated preference work and specifically patient centricity in healthcare has had in the last few years—people still don't quite understand what we do and get confused between stated preference studies and patient-reported outcomes studies. But we're making progress."

One sign of this progress Dr. Johnson points to is the adoption of guidance for submitting patient preference data, specifically for benefit-risk assessments, at FDA's Center for Devices and Radiological Health. "But the Center for Drug Evaluation and Research (CDER) is moving in that direction much more slowly," he says. "And until we can get actual guidance from CDER, it's still going to be hard to see much of a role that quantitative patient preferences are going to have in regulatory assessments of drugs."

However, Dr. Johnson believes that CDER will get there, and sooner rather than later. "Becky Noel [Global Leader for Benefit-Risk Assessment at Eli Lilly] once said to me about 15 years ago when we were working on the Tysabri studies, that it took 10 years for any major changes to take place at the FDA," he says. "A few years ago I asked Becky whether she thought the clock had started yet. But it had, it had. So maybe we are about 5 years away, 4 years away from seeing those kinds of changes in the CDER."

His current research involves quantifying patients' willingness to accept side-effect risks in return for therapeutic benefits and estimating general time equivalences among health states.

"We are actively involved in adapting these general population or general patient population surveys for use in a clinical setting," Dr. Johnson says. "And the idea is to come up with a preference diagnostic tool that can be used quickly, efficiently, and in a clinical setting—maybe when patients are in the waiting room before an

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appointment—that would provide the physician with diagnostics roughly like vital signs diagnostics that they routinely receive." Physicians already try and obtain that information informally but have very limited time and resources to do so. "It's the informally part that makes us all nervous, because there's just limited time and resources to spend with patients," Dr. Johnson says. "We'd like to formalize that to some extent with a validated instrument that would actually produce, in a more structured way, what physicians and other caregivers do more informally."

### A LOVE FOR SINGING AND SCANDINAVIAN CULTURE

Although Dr. Johnson focuses mostly on his work, he does enjoy choral singing, being part of the first tenor section in various local groups. His wife is a choral conductor, which he says allows them to share that interest.

He admits he does not perform as often as he used to. "I've actually slowed down a little bit," Dr. Johnson says. "A couple of years ago, between church and the various community groups I sang with, I was doing maybe 10 or 12 concerts a year, with about 5 or 6 with them during the Christmas season. But now it's more like 4 in total. That's a little more reasonable!"

As a Mormon missionary in the 1960s in Sweden, Dr. Johnson developed an affinity for the country. He learned Swedish and has brought his family back to Sweden several times, and they share his love of Scandinavian culture.

One of his family's traditions is holding a traditional Swedish "Other Day of Christmas" celebration, which is the day after the holiday. "We have a big party every year in our home, with Swedish music and a Christmas tree decorated in a traditional Swedish way, and we do dancing around the Christmas tree," Dr. Johnson says.

As he has cut back his choral group involvement, Dr. Johnson has concentrated on work. He continues to establish ways to validate preference data.

"I think we've made some progress in establishing some standards for doing these kinds of studies, in establishing validity tests that establish whether the data we have could stand up to the standard expectations about evidence," he says. "But it's hard to do this well, it's hard to do it at all—there aren't the resources available that are obviously available for other kinds of data collection in health.

So yes, it feels good to have gotten this far but it really feels like we have a long way to go."

## ISPOR SCIENTIFIC ACHIEVEMENT AWARDS

# Call for Nominations

The ISPOR Awards Program is designed to foster and recognize excellence and outstanding technical achievement in pharmacoeconomics and outcomes research. These awards will be presented at ISPOR 2019, May 18-22, 2019, New Orleans, LA, USA.

**The ISPOR Avedis Donabedian Outcomes Research Lifetime Achievement Award | Nominations Due by December 7, 2018**

The ISPOR Avedis Donabedian Outcomes Research Lifetime Achievement Award was established in honor of the late Avedis Donabedian MD, MPH to acknowledge those individuals who have made a major contribution to the improvement of health outcomes. Nominations may be made by any ISPOR member. Members may nominate more than one person; however a completed letter of recommendation must accompany each nomination.

*For complete details on background, criteria, selection process, and nature of the award, see: https://tinyurl.com/yba48czc.*

**ISPOR Marilyn Dix Smith Leadership Award | Nominations Due by December 7, 2018**

The ISPOR Marilyn Dix Smith Leadership Award is international in scope and stature. The Award recognizes one individual each year that has provided extraordinary leadership to the Society. Nominations for the Marilyn Dix Smith Leadership Award require a letter of recommendation for the nominee, nominee's leadership contributions to the Society and nominee's CV.

*For complete background, criteria, selection process, and nature of the award, see: https://tinyurl.com/y7hm6pak.*

**ISPOR Bernie O'Brien New Investigator Award | Nominations Due by February 9, 2019**

The ISPOR Bernie O'Brien New Investigator Award was established in 2004 to honor the long-standing commitment of Bernie J. O'Brien, PhD to training and mentoring new scientists in the fields of outcomes research and pharmacoeconomics. All nominations must include a letter of support for the nominee and a current edition of the nominee's CV essay indicating the reason for your nomination.

*For complete background, criteria, selection process, and nature of the award, see: https://tinyurl.com/ybh7zjmd.*

**ISPOR Award for Excellence in Methodology and Application in Pharmacoeconomics and Health Outcomes Research ISPOR Nominations Due by February 8, 2019**

The ISPOR Award for Excellence in Methodology and Application in Pharmacoeconomics and Health Outcomes Research were established in 1997 to recognize outstanding research in the field of pharmacoeconomics and outcomes research methodology and outstanding practical application of pharmacoeconomics and outcomes research in health care decision making. Only ISPOR members may submit nominations (either their own publications or others). All nominations must include a brief cover letter indicating the reason for the nomination. Supporting documentation MUST include a PDF of the nominated paper.

*For complete background, criteria, selection process, and nature of the award, see: https://tinyurl.com/y9mdxza3 and https://tinyurl.com/yb5s7f8y.*

**Nominations should be sent to: awards@ispor.org**

## HEOR NEWS

A diverse collection of relevant news briefs from the global HEOR (health economics and outcomes research) community.

### 1 Europe Ready to Cash in on Cheap Copies of AbbVie Biotech Drug (PharmaLive/Reuters)

US drug maker AbbVie faces a crunch moment in Europe in mid-October when less-expensive copies of its $18-billion-a-year biologic drug Humira—the world's best-selling prescription medicine—hit the market. With vast sums at stake, European healthcare administrators say they will waste no time in exploiting the situation to drive down drug bills. "The opportunity is too big miss," said Jatinder Harchowal, one of the coordinators of Britain's push for greater use of cheaper biotech drug copies (known as biosimilars) and chief pharmacist at the Royal Marsden hospital.

http://www.pharmalive.com/europe-ready-to-cash-in-on-cheap-copies-of-abbvie-biotech-drug/

### 2 Eli Lilly CEO: Why Consumers Are Key to Bringing Down Healthcare Costs (Forbes)

For all of us who want better value in healthcare, seeing Apple, Amazon, and other tech companies deploy record profits to transform delivery of medicines and medical services should be good news. But there's one big barrier standing in the way: the outdated US healthcare system. Without significant reforms, these companies' efforts—and many investors' hopes—could fail.

http://fortune.com/2018/08/27/eli-lilly-health-care-pharmaceuticals/?utm_source=NPC+Contact+List&utm_campaign=e9df3cf67e-EMAIL_CAMPAIGN_2018_08_27_06_24_COPY_01&utm_medium=email&utm_term=0_3ddd3927eb-e9df3cf67e-198281001

### 3 Key Senate, House Lawmakers Tell HRSA to Do Its Work on 340B (Modern Healthcare)

After months of oversight and legislative hearings, key House and Senate lawmakers say the Health Resources and Services Administration needs to work with its current resources before Congress grants the agency more authority over the 340B drug discount program—from fining drug makers who knowingly overcharge 340B hospitals to determining how to set ceiling prices for drugs.

http://www.modernhealthcare.com/article/20180827/NEWS/180829912

### 4 John Arnold: Are Pharmacy Benefit Managers the Good Guys or Bad Guys of Drug Pricing? (STAT News)

This model has generated significant criticism lately for good reason. Commercial insurers complain that pharmacy benefit managers are not passing through the rebate revenue they should. In Medicare, the Medicare Payment Advisory Commission has consistently raised concerns that pharmacy benefit managers are not choosing the lowest-cost drugs. And recent work by 46brooklyn suggests that pharmacy benefit managers are charging Medicaid managed care organizations much more for generic drugs than they are paying pharmacies. So where did pharmacy benefit managers go wrong? In three areas: consolidation, rebate revenue, and transparency.

https://www.statnews.com/2018/08/27/pharmacy-benefit-managers-good-or-bad/?utm_source=NPC+Contact+List&utm_campaign=e9df3cf67e-EMAIL_CAMPAIGN_2018_08_27_06_24_COPY_01&utm_medium=email&utm_term=0_3ddd3927eb-e9df3cf67e-198281001

### 5 NICE Rejects Perjeta in Post-Surgery Breast Cancer Use – Again (pharmaphorum)

NICE has continued to reject Roche's Perjeta (pertuzumab) in its use to prevent early-stage HER2-positive breast cancer from recurring after surgery, after reconsidering evidence in the light of changes to the cost of the drug combination. The new first draft guidance considers corrections to the costs of administering the drugs, and the impact of cheaper biosimilar trastuzumab—a near copy of Roche's Herceptin—on reducing the overall cost of the adjuvant Perjeta regimen.

https://pharmaphorum.com/news/nice-rejects-perjeta-in-post-surgery-breast-cancer-use-again/

### 6 How to Tame Healthcare Spending? Look for 1% (The New York Times)

The healthcare system in the United States costs nearly double that of its peer countries, without much better outcomes. Many scholars and policymakers have looked at this and dreamed big. Maybe there's some broad fix—high deductibles, improvements in end-of-life care, a single-payer system—that can make United States health care less expensive. But what if the most workable answer isn't something big, but hosts of small tweaks? A group of about a dozen health economists has begun trying to identify policy adjustments, sometimes in tiny slices of the health care system, that could produce savings worth around 1% of the country's $3.3 trillion annual health spending. If you put together enough such fixes, the group points out, they could add up to something more substantial.

https://www.nytimes.com/2018/08/27/upshot/rising-health-care-costs-economists-propose-small-solutions.html

## RESEARCH ROUNDUP

Section Editors: **Gabriela Tannus Branco de Araujo, MSc** and **Marcelo Fonseca, MD, MSc**

*Editors Note: The following text is a simplified summary of the published article. They do not contain an opinion or an in-depth analysis on the results obtained by the authors of said articles. The selection of these works was made based on theme relevance, not a product of a literature review or of a methodological quality selection.*

**In this issue of *Value & Outcomes Spotlight*, we highlight for our readers aritcles of great relevance for those who work in HEOR. We recommend that you read and critically review this article.**

# EUPATI and Patients in Medicines Research and Development: Guidance for Patient Involvement in Regulatory Processes

**Haerry D, Landgraf C, Warner K, et al.**
*Front Med (Lausanne)*. 2018 August 17;5:230.

In September 2018, the European Patients' Academy on Therapeutic Innovation (EUPATI) published an article related to a proposal regarding the involvement of patients in HTA projects.

Patients' participation in the health analysis and decision-making process has grown significantly in recent years, mainly in Europe, and EUPATI is proposing a format in which the patient have a direct participation in the processes of health technologies research and assessment.

The article brings the EUPATI suggestion of how to involve patients in HTA activities, through a flow of activities and when and how to involve patients in the assessment process. For those who work in the HEOR area, knowledge of this flow of patient involvement can positively impact the construction of studies, especially in countries where the concept of value-based health care is already more present in discussions with payers.

EUPATI also brings a proposal of how and where the patient can be involved in the medicines R&D process. For HEOR, the understanding of the form and when the patient can be involved also creates the opportunity to perform real world data studies and where their results would be best used across the process.

The publication also brings a consensus held among Patient organizations, academia, HTA agencies and industry about what would be a proposal of work practices would be considered as high value based on relevance, fairness, equity, legitimacy and capacity building.

CONFERENCES & EDUCATION

# Barcelona: Showcase of Health Systems in the 21st Century

**Sarah Garner, PhD**, World Health Organization, Geneva, Switzerland; **Zoltan Kalo, PhD**, Eötvös Loránd University, Syreon Research Institute, Budapest, Hungary; **Guillem López-Casasnovas, PhD**, Universitat Pompeu Fabra, Barcelona, Spain, ISPOR Europe 2018 Conference Proram Co-Chairs

We are very pleased to host ISPOR Europe 2018 in Barcelona, Spain. ISPOR returns to Barcelona 15 years after it's last event in the capital of Catalonia. Given constant changes in the healthcare landscape including the exponential impact of digital and genomic revolutions, this year's theme, "**New Perspectives for Improving 21st Century Health Systems**" is especially timely. The call to join to address needed improvements in healthcare assessment and delivery has never been stronger; but disparities in process and priorities make the complexity of joint action seem insurmountable. Advancing views on joint assessment process including how to define value within differing local definitions of 'what is fair and equitable' raise vital questions that will be addressed in plenary sessions, issues panels, workshops, and research presentations.

The first plenary, on Monday, 12 November, "**Joint Assessment of Relative Effectiveness: "Trick or Treat" for Decision Makers in EU Member States**," features a diverse panel which will examine the role of joint clinical assessments and discuss the risks and benefits of moving beyond the status quo in health technology assessment processes in Europe.

The second plenary, on Tuesday, 13 November, "**Pharmaceutical Pricing: The Many Faces of Fairness**," will focus on defining "fair" in the context of pharmaceutical pricing. Speakers will also explore whether it is possible (or necessary) to come to a shared understanding of fairness.

On Wednesday, 14 November, the third and final plenary, "**Budget Impact and Expenditure Caps: Potential or Pitfall?**," will address several questions around the budget impact of health policies, including whether a budget-capping strategy encourages or undermines the achievement of better health outcomes, in both the short and the long term, in a way consistent with overall societal goals.

These plenaries, along with our outstanding short course program, topical issue panels, workshops, and research presentations provide extra incentive to attend.

Garner

Kalo

López-Casasnovas

As noted at www.spain.info, Barcelona is a Mediterranean and cosmopolitan city with Roman remains, medieval quarters and the most beautiful examples of 20th century Modernism and avant-garde. It is no surprise that emblematic constructions by the Catalan architects Antoni Gaudí and Lluís Doménech i Montaner have been declared World Heritage Sites by UNESCO. The city's origins are Roman, and its long history and economic dynamism have made Barcelona a cultural city, which can be seen in the historic-artistic heritage and the promotion of the most innovative artistic trends. Strolling around the streets of Barcelona will bring surprises at every turn. Pedestrian streets in the old quarter, green spaces, and a splendid seafront with a range of modern facilities reflect its multi-faceted character. Barcelona has cleverly succeeded in embracing its past without forgetting its commitment to the future.

In 1992, Barcelona hosted the Olympic Games. It was a great opportunity to improve the city. Many new parks were opened and other significant changes to the city were made. One example is opening the new beaches in the Poble Nou area. Finally, Barcelona is home to football team FC Barcelona.

We look forward to meeting with all of you to rededicate ourselves to ISPOR's mission to promote HEOR excellence to improve decision making for health globally.

See you in Barcelona!

***REFERENCE***

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## FROM THE JOURNALS

# The following highlighted articles appear in the September and October 2018 issues of *Value in Health* and the October 2018 issue of *Value in Health Regional Issues.*

For more information on *Value in Health*, visit: https://www.ispor.org/publications/journals/value-in-health.
For more information on *Value in HealthRegional Issues*, visit: https://www.ispor.org/publications/journals/value-in-health-regional-issues.

## *Value in Health* September 2018

### ISPOR REPORTS

**Application of Constrained Optimization Methods in Health Services Research: Report 2 of the ISPOR Optimization Methods Emerging Good Practices Task Force**

*This second report from the ISPOR Optimization Methods Emerging Good Practices Task Force focuses on the application of these methods and discusses a number of case studies.*

### Editorial

**Are We Ready for Healthcare Resource Allocation Using Constrained Optimization Methods?**

Stephanie Earnshaw

### THEMED SECTION: SEQUENCING TECHNOLOGIES

**Uncertainty and the Under-Valuation of Services for Severe Health States in Cost Utility Analyses**

*The September 2018 issue features a themed section on sequencing technologies, edited by Kathryn Phillips. This themed section included 5 papers, plus an editorial, and discusses a number of issues discussing various aspects of valuation, including the methodological issues, measurement of health and non-health outcomes, the use of 'big data' and the analysis of costs.*

### Editorial

**Assessing the Value of Next-Generation Sequencing Technologies: An Introduction**

Kathryn Phillips

### Articles

**Methodological Issues in Assessing the Economic Value of Next-Generation Sequencing Tests: Many Challenges and Not Enough Solutions**

Kathryn Phillips, Patricia Deverka, Deborah Marshall, Sarah Wordsworth, Dean Regier, Kurt Christensen, James Buchanan

**Valuation of Health and Non-Health Outcomes from Next-Generation Sequencing: Approaches, Challenges, and Solutions**

Dean Regier, Deirdre Weymann, James Buchanan, Deborah Marshall, Sarah Wordsworth, Sarah

**Using 'Big Data' in the Cost-Effectiveness Analysis of Next-Generation Sequencing Technologies: Challenges and Potential Solutions**

Sarah Wordsworth, Brett Doble, Katherine Payne, James Buchanan, Deborah Marshall, Christopher McCabe, Deann Regier

**Cost Analyses of Genomic Sequencing: Lessons Learned from the MedSeq Project**

Kurt Christensen, Kathryn Phillips, Robert Green, Dmitryr Dukhovny

**From the Past to the Present: Insurer Coverage Frameworks for Next-Generation Tumor Sequencing**

Julia Trosman, Christine Weldon, William Gradishar, Al Benson III, Massimo Cristofanilli, Alison Kurian, James Ford, Alan Balch, John Watkins, Kathryn Phillips

## *Value in Health* October 2018

### ISPOR REPORTS

**Economic Analysis of Vaccination Programs**

Josephine Mauskopf, Baudouin Standaert, Mark Connolly, Anthony Culyer, Louis Garrison, Raymond Hutubessy, Mark Jit, Richard Pitman, Paul Revill, Johan Severens

*This report provides recommendations for budget holders and decision makers in high-, middle-, and low-income countries requiring economic analyses of new vaccination programs to allocate scarce resources given budget constraints.*

### Editorial

**Vaccination Programs: Economic and Leadership Considerations**

Kenneth Hartigan-Go

## *Value in Health Regional Issues* October 2018

### THEMED SECTION: DRUG POLICY

*In this volume we publish the second part of a theme section on Drug Policies in Central and Eastern Europe. The project was initiated and conducted by the ISPOR Central and Eastern European (CEE) Publication Network working group.*

### Editorial

**Drug Policy Research and Health Technology Assessment in Central and Eastern Europe, Western Asia and Africa: The Interface between Research Evidence, Policy, and Practice**

Ahmed Awaisu, PhD, BPharm

### Articles

**Drug Policy in Estonia**

*Marika Lepaste*

**Drug Policy in Greece**

*John Yfantopoulos, Athanasios Chantzaras*

**Drug Policy in Romania**

*Ciprian-Paul Radu, Bogdan Cristian Pana, Florentina Ligia Furtunescu*

**Drug Policy in Central and Eastern Europe – Russian Federation**

*Malwina Holownia-Voloskova, Pavel Vorobiev, Maxim Grinin, Maria Davydovskaya, Tatiana Ermolaeva, Konstantin Kokushkin*

# How mHealth Technology Is REVOLUTIONIZING Clinical Research

By Michele Cleary

With the entry of technology giants into the digital health market, big changes are on the horizon for clinical research

This September, Apple once again dominated the world's daily news cycle with its latest product launch with not only its latest iPhone but also its newly enhanced Apple Watch—a connected device that includes an FDA-approved ECG. Apple's participation in this sector—the connected biosensor market—demonstrates the enormous appeal and profit potential these devices hold. As technology superpowers like Apple turn their innovation talents to developing connected biosensors, new products are changing clinical research, offering real opportunities to improve research data, enhance trial efficiency, and reduce costs.

As technology superpowers like Apple turn their innovation talents to developing connected biosensors, new products are changing clinical research, offering real opportunities to improve research data, enhance trial efficiency, and reduce costs.

## THE EVOLUTION OF mHEALTH

Over the past decade, digital health innovations have revolutionized healthcare delivery with solutions ranging from telemedicine services to electronic medical record software. Thanks to the innovation of mobile digital health services, commonly referred to as mHealth products, the clinical research environment now faces its own revolutionary moment with new challenges and opportunities.

Traditional clinical trials are being transformed into 'smart RCTs' by adding mHealth apps. Using tools such as Apple's Researchkit and the Google Study Kit, researchers can create custom mHealth apps specific to their clinical trials, which improve clinical trial operations by accelerating study recruitment, simplifying patient reporting, and enhancing participant engagement.

Now, connected mHealth biosensors are further revolutionizing clinical trials by allowing a real-time view of real world events.

Embedded within a wearable device, unobtrusive mHealth biosensors can continuously collect data throughout the patient's daily routine, objectively detecting disease-related physiological or behavioral biomarkers and relaying data back to researchers. These products represent a significant improvement over patient self-reported diaries and earlier monitoring devices.

Most importantly, mHealth innovation—through apps and biosensors—represent a patient-centric approach to clinical trial design. These products empower patients, allowing them the opportunity to participate fully in clinical research without shackling them to devices that impede their daily lives.

Currently, mHealth biosensors collect a wide range of physiological data, including blood pressure, posture, heart rate, electrodermal activity, pulse oximetry, and sleep patterns. As disease-specific algorithms embedded within these devices continue to improve, these sensors improve their ability to differentiate between disease-related bio-measures and normal variation, increasing their 'signal-to-noise' ratio, to better identify disease presence or disease progression.

## SPECIFIC BENEFITS TO CLINICAL RESEARCH

The potential impact of mHealth biosensors on clinical research stems largely from their ability to provide more contextual, timely data with minimal burden on study participants. These products can improve clinical research in 3 key areas: data collection, analysis, and study operations.

### DATA QUALITY BENEFITS

*• Collection of real-world data: mHealth biosensors fills the gaps between research assessments or episodes-of-care by providing contextual data on patients' daily lives. With such an enormous volume of real-world data, companies can refine their understanding of drug efficacy, enabling them to identify which types of patients are most receptive to the product and under which conditions. Such continuous measurement through an unobtrusive sensor can minimize the impact of the Hawthorne effect (changes in behavior stemming from observation), creating a more representative view of patient disease and treatment effects.*

*• More accurate data: mHealth biosensors' consistent, passive data collection mean that far more clinical events are captured, not just those that participants choose to report. These sensors also provide more objective data, eliminating patient interpretation as to whether a given clinical event is 'reportable,' thus minimizing the variability in outcome data.*

*• Deliver more timely data: Thanks to mobile data reporting, researchers can have near real-time access to patient data. More immediate access to data allows researchers to identify potential adverse events quickly. It can also help quickly identify subsets of patients for whom a product may be more effective. Rapid identification of emerging issues can empower companies with the information needed to respond quickly to unexpected outcomes, alleviating potentially dangerous patient events. Equipped with this information, companies can decide more quickly whether to restructure future studies or even whether to proceed with more trials.*

*• Identification of novel endpoints: The enormous volumes of data associated with mHealth studies may also help identify novel endpoints not previously observable in traditional clinical trials. These novel endpoints could, in turn, define better targets for early treatment intervention. As these novel endpoints undergo validation and as further research establishes their link to important health outcomes, these endpoints may even replace traditional in-clinic endpoints in future research and submissions.*

> mHealth innovation–through apps and biosensors–represent a patient-centric approach to clinical trial design.

*Novel endpoints represent a critical step towards more patient-centric trials. mHealth biosensors collect more of the real-world outcomes most relevant to patients, as opposed to focusing solely on the biomarkers most relevant to clinical pharmacologists. The ability to capture these endpoints help drives clinical research towards more real-world investigations.*

*The identification of such novel endpoints is particularly important in conditions with a low signal-to-noise ratio. For instance, the study of some neurodegenerative diseases is limited given the difficulty in observing 'gold standard' metrics within a trial setting. Novel endpoints may advance clinical research for such conditions, improving treatment options and health outcomes in these patients.* >

## METHODOLOGICAL BENEFITS

By providing enormous volumes of research data cost-effectively, mHealth sensors can improve 2 significant methodological challenges often experienced with real-world data:

- Signal-to-noise ratio
- Variability across participants

Low signal-to-noise ratio is not uncommon, especially during early disease stages. With sporadic clinical assessments and standard patient diaries, traditional clinical trials struggle to collect sufficient data to clearly differentiate treatment effects (signal) from normal behavior (noise).

Deborah Kilpatrick, PhD, CEO at Evidation Health, a health and measurement company on the leading edge of mHealth biosensor use in clinical trials, recognizes an enormous opportunity to remedy these challenges through mHealth sensors. "These (challenges) are not new to clinical research. But the way we can now deal with them in the digital era is massively aided by faster, better, cheaper and bigger digital datasets that can be continuously and frictionlessly collected."

According to Dr. Kilpatrick, as data sensors become more integrated into our daily lives, there is a risk of lowering the signal-to-noise ratio just due to the "noise" of so much variability outside clinic walls. However, the richness of continuously flowing datasets over time can mitigate this risk by finding disease signals that were simply not possible before to measure.

The second issue is the individual variability in the data—each patient is different, especially at early stages of a disease. In an ambulatory, real-world environment, there will be a great deal of variability in biomarkers from patient to patient as compared with a more severe population where the disease signal is much stronger and more concentrated.

Being able to collect large volumes of longitudinal, continuous data from very early state to advanced disease in the same set of patients allows for patients to effectively become their own control—which is enabled because the data are cheaper to obtain continuously over long periods of time.

## OPERATIONAL BENEFITS

Finally, mHealth biosensors have the capacity to improve clinical trial operations by lessening the burden of trial participation and by making the trial process more cost effective.

• *Lessening the burden of trial participation: mHealth biosensors are inherently patient-centric, maximizing patient engagement by minimizing the burden of trial participation.Passive data collection causes minimal disruption to patients' daily routines as compared to the demands of traditional clinical trials, which often require frequent clinic visits and patient reports via daily diaries. And lessening the burden of study participation would likely improve participant retention rates, thereby improving both the quality and the quantity of study data.*

Finally, minimizing the burden of trial participation could potentially increase the participation rates of underrepresented groups. For some patients (eg rural, elderly, low income), trials requiring frequent clinic visits may be impossible due to the cost or complexity of transportation. And for English language learners, patient diaries may be too complicated to consider study participation. Trials using mHealth sensors removes many of these barriers.

• *More cost-effective trials: With vast data resources accrued through mHealth biosensors, researchers can more readily identify patient subsets in whom treatment effects may be suboptimal, allowing companies to shorten certain clinical trials or refine future studies to target more appropriate subgroups. Adverse events could also be identified more readily than traditional methods, allowing for more rapid intervention and avoiding costs associated with widespread adverse events.*

> Equipped with more real-world data, perhaps even data on novel endpoints, companies can make more informed decisions regarding whether to proceed with further drug trials and avoid the enormous expense of failed trials.

Finally, companies could benefit tremendously with additional data insight that could clarify their risk of failure in future trials. Traditional clinical data streams with traditional endpoints are often insufficient to predict the risk of failure in future trials, which may explain why nearly 60% of phase II clinical trials end in failure. [1] But equipped with more real-world data, perhaps even data on novel endpoints, companies can make more informed decisions regarding whether to proceed with further drug trials and avoid the enormous expense of failed trials.

## CHALLENGES SURROUNDING MHEALTH BIOSENSORS IN RESEARCH

While mHealth biosensors allow researchers to better understand disease progression and treatment effects by using real-world, real-time data, their use in clinical research is not without challenges. Potential impediments include:

• *Infrastructure Requirements:* Continuous monitoring leads to enormous volumes of data, requiring significant information technology infrastructure. Some companies now support digital biosensor technology in clinical trials by collecting data remotely, and connecting data to other data attributes.

• *Data Security:* As with any connected devices, data security presents ongoing challenges. Necessary process and technical applications are integral to protecting data transmittals.

• *Accuracy and Reliability:* The accuracy and reliability of digital biomarker will need to be supported by evidence that demonstrates its specificity, sensitivity, and positive and negative predictive values.

• *Validation:* Perhaps the most challenging aspect of digital biosensors for clinical research is the question of validity—can these products perform a valid measure of the targeted biomarker as compared with the gold standard? Would comparisons even be appropriate? Are continuous measures of clinical attributes better than discrete measures? Do more novel measures better at identifying individuals at risk? Do they identify clinically meaningful events?

## THE REGULATORY RESPONSE TO mHEALTH

Regulatory agencies in both the US and in Europe are scrambling to develop suitable regulations for digital health products.

In late 2017, the FDA introduced the Digital Health Innovation Action Plan as a way to spur digital health innovation, expanding opportunities for digital health tools to be incorporated into drug review. By April 2018, the FDA outlined its approach to digital health.

"If we want American patients to benefit from innovation, FDA itself must be as nimble and innovative as the technologies we're regulating," says FDA Commissioner Scott Gottlieb, MD. [2] Commissioner Gottlieb presented the FDA's vision of a regulatory framework that would open a more efficient path to review and approval for digital health tools as part of drug review, thus ensuring that these tools reach their full potential to help us treat illness and disease, while meeting the FDA's high standard for safety and effectiveness.

In September of this year, Commissioner Gottlieb announced that the agency's FY2019 budget would include a Center of Excellence for Digital Health that would advance modernizing our regulatory approach to digital health, thus helping this industry grow, while protecting patients. Says Dr. Gottlieb, "This Center of Excellence would help establish more efficient regulatory paradigms, consider building new capacity to evaluate and recognize third-party certifiers and support a cybersecurity unit to complement the advances in software-based devices." [3]

Meanwhile, the European Medicines Agency (EMA) has yet to issue general guidance on the subject. "At the present stage of knowledge and technology development, data collected in this manner are mainly envisaged to provide supportive evidence to clinical or functional claims, rather than constitute the main body of evidence to support regulatory approval," says Francesca Cerrata, MSci, MPharm, Senior Scientific Officer, European Medicines Agency.

However, EMA has released several qualification advices on specific proposals, including the use of a novel methodology in the context of research and development, such as ingestible sensors. [4]

In both the United States and Europe, the regulatory landscape will continue to evolve in coming years.

## WHAT MIGHT THE FUTURE HOLD FOR mHEALTH TRIALS

The era of mHealth-informed clinical trials is in its early stages.

Researchers are currently developing methods to contend with digital biomarker discovery. And they are developing ways to deal with the consumer-grade data streams, and not just clinical grade data streams. "We're doing rigorous studies just like the molecular companies were doing with genomic data a decade ago to identify which biomarkers can be developed and validated and actually have relevance." says Dr. Kilpatrick.

The regulatory world is still composing its guidelines for companies regarding how they will review mHealth data in their approval processes. It is unclear how technology companies, coming from a world that rewards bold designs and rapid innovation will thrive in the heavily regulated world of drug development. How will this change in corporate culture impact innovation?

And how will new sensor technology impact drug trials? mHealth sensors are becoming more resilient to environmental variations, expanding their potential for real-world data collection. Reductions in sensor size and power needs coupled with algorithm improvements will ease battery requirements, making biosensors less obtrusive and more easily integrated into patients' daily life, allowing for even greater data. New sensor technologies, such as silicon-based microneedles, will continue to expand the potential for new types of clinical studies. [5]

Beyond clinical trials, mHealth sensors could be enormously beneficial to clinical practice. Additional real-world data could help providers better evaluate disease progression and treatment effects in their patients, equipping providers with the tools needed to deliver more personalized medicine. mHealth sensors could deliver the data needed to help providers identify optimal treatment at the best time for each patient, ISPOR is helping to facilitate the discussion regarding how these devices may improve research. Last May's US ISPOR meeting, titled "Real-World Evidence, Digital Health, and the New Landscape for Health Decision Making," provided a great opportunity for researchers and decision-makers to discuss digital health and its role in patient-centered outcomes research. [6]6 Workshops included discussions on how to better meet end-user needs, how to support the adoption of digital health, and how to communicate value.

Yet questions remain—will patients be willing to wear such devices? Will payers be willing to pay for them? Will providers be able to wade through the influx of data?

These are early days. But as we learn how best to integrate mHealth biosensors into research, these devices not only hold the promise to make trials faster, safer, and more cost-effective. They could help illuminate novel endpoints that may help deliver more individualized care to patients everywhere.

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*About the Author: Michele Cleary is an HEOR researcher and scientific writer with more than 15 years of experience in the healthcare field.*

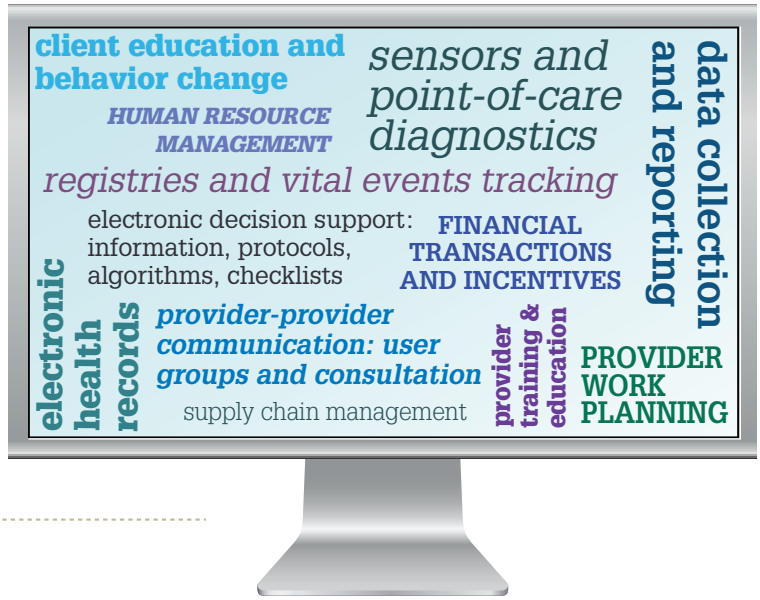
# By the Numbers: mHealth/Digital Health

Section Editor: The ISPOR Student Network

## APPLICATIONS OF MOBILE HEALTH[1]

**Mobile Health is being used:**

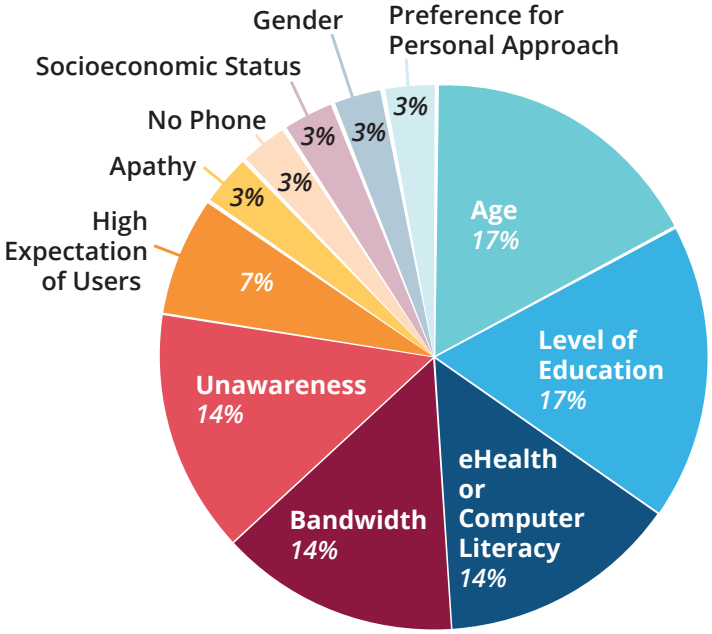
1. For patient communication, monitoring, and education
2. To reduce the burden of diseases linked with poverty
3. To improve access to health services, clinical diagnostics, and treatment adherence
4. For chronic disease management




## Timeline of Country Adoption of eHealth Policies or Strategies (1990-2015)[2]

| | |
|---|---|
| 1990 | San Marino |
| 1995 | Finland |
| 1996 | Norway |
| 2000 | Canada |
| 2003 | Estonia, Malawi, Singapore |
| 2004 | Republic of Moldova |
| 2005 | Latvia, Sudan, USA |
| 2006 | Italy, Luxembourg, Malaysia, Vietnam |
| 2007 | Cabo Verde, Switzerland |
| 2008 | Australia, Mongolia |
| 2009 | Iceland, Jordan, Uzbekistan |
| 2010 | Azerbaijan, Ghana, Lithuania, New Zealand, Sweden, Turkmenistan |
| 2011 | Georgia, Kenya, Maldives, Poland |
| 2012 | Armenia, China, Costa Rica, Cote D'Ivoire, Iran (Islamic Republic of), Netherlands, South Africa, Uganda, United Kingdom, Uruguay, Zimbabwe |
| 2013 | Belgium, Cyprus, Greece, Ireland, Jamaica, Kazakhstan, Mali, Philippines, Russian Federation, Ukraine, Zambia |
| 2014 | Argentina, Bhutan, Bulgaria, Chile, Democratic People's Republic of Korea, Dominican Republic, Ethiopia, Gambia, Japan |
| 2015 | Bangladesh, Paraguay, Qatar, Rwanda |

## Main Barriers for Patients Regarding the Implementation of Telemedicine Globally[3]

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# Oncology Value Framework in the Era of Digital Health Technology: A Patient-Centric Approach

**Won Chan Lee, PhD**; **R. Scooter Plowman, MD, MBA, MHSA**; **George M. Savage, MD, MBA**, Proteus Digital Health Inc, Redwood City, CA, USA

## KEY POINTS

Oncology health apps have a great potential to be widely adopted by healthcare systems, payers, pharmacy benefit managers, specialty pharmacies, and drug manufacturers in the coming years.

Optimal digital health solutions should ultimately seek to bridge the current patient-clinician communication gaps, particularly for symptom management outside of the immediate care environment. Achieving this reduces unnecessary clinical visits, particularly to emergency department and hospitals.

Digital health technologies can fill current gaps in delivering care to oncology patients, constructively disrupting the current health delivery environment while rebalancing the existing oncology value framework.

## RISING TIDE IN THE SEA OF DIGITAL HEALTH APPLICATIONS

They are within easy reach. They are ubiquitous. Intertwined within mobile devices, they enable access to timely health information and care team communication, mimicking behavioral coaches. Indeed, digital health technologies and health applications ("apps") have begun transforming the modern healthcare ecosystem. According to IQVIA, more than 318,000 health apps and 340 consumer-wearable devices are now available worldwide, with more than 200 health apps being added each day.[1] While there are myriad apps focusing primarily on chronic care management, such as diabetes, hypertension, and asthma, more than 1000 oncology-specific apps are already available.[2]

> It is an ideal time for digital health technologies to assume a value-based role in generating sufficient clinical, real-world evidence demonstrating improved patient care, and quality of life and satisfaction while reducing healthcare costs.

These oncology-focused digital technologies attempt to address the various needs of cancer patients and their care communities. Many focus on disease management, while some promote side effect reporting and others address survivorship. Most of these apps and tools are not seeking approval through the US Food and Drug Administration (FDA) regulation or pursuing interoperability with electronic medical records (EMRs). As such, patients, caregivers, and care teams find it confusing to distinguish toys and tools from treatments and medical devices. The current flood of new entrants into the oncology care paradigm fails to complete the communication loop linking patients and their clinicians. Many oncology patients and caregivers are increasingly burdened by assuming the role of nurses as they care for themselves or loved ones. From the time of filling and taking prescriptions until their next clinical visit, many challenging clinical decisions may arise for patients. Between visits, there is a dearth of communication, with most interactions initiated by patient and caregiver. Almost nowhere is this problem more pronounced than with oral oncolytics. In the growing transition from intravenous (IV) to oral chemotherapy, many patients are left to their own devices when navigating the often complex dosing regimens, challenging and sometimes debilitating side effects, and complicated prognostic criteria. Considering that 8 out of the 14 new active substances launched in 2017 for oncology were oral therapies, these concerns are not trivial.[2]

New entrant apps, those in development, and the incumbents gaining in popularity claim to address pieces of this fragmented communication chain. Telemedicine and virtual patient visits have become increasingly common, especially for those who live in remote areas or for postsurgical patients less able or willing to travel long distances. Particularly for symptom management outside of the immediate care environment, digital and mobile outreach are becoming commonplace. Such digital solutions offer even more potential when the data captured in the apps are shared with care teams and integrated into EMRs. This offers clinicians easy access to relevant and timely patient health data to inform appropriate and opportune interventions. Based on the intrinsic value that can be captured by the current oncology care environment, these connected health apps have a great potential to be widely adopted by healthcare systems, payers, pharmacy benefit managers, specialty pharmacies, and drug manufacturers in the coming years. There seems to be "a rising tide" in the digital era of oncology care delivery. A key question remains: How will digital health technologies fit into the value stream in the current US oncology care models? >

## CURRENT GAPS IN THE ONCOLOGY VALUE ASSESSMENT FRAMEWORKS

How is the value of oncology care or oncolytic therapy being evaluated in the US healthcare environment? For cancer care in particular, assessing "value" has long been a conundrum. Several countries ascribe to quality-adjusted life year (QALY) benchmarks to define thresholds of value by which to justify scarce resource allocations. Yet, value varies by stakeholder and is inherently individual. There is a divergence of views because perceived value depends on the evaluating stakeholders, unique characteristics of patients and caregivers, and how the evidence of value is captured. Given the strain that oncology costs are placing on the overall healthcare value chain, there is a clear need to refine the value assessment frameworks (VAFs). According to recent estimates from the National Cancer Institute, cancer care-related costs are projected to grow by 39% ($172.8 billion) by 2020.[3] Cancer drug spending was estimated at $37.8 billion in 2016, representing a 33% increase ($9.4 billion) for new drugs alone since 2010.[4]

Beginning around 2010, the increasingly high cost of oncology drugs and obvious trend toward precision medicine resulted in greater value, and subsequent interest in the development and application of cost-effectiveness tools and VAFs. These have focused mostly on payers and providers at large health systems and integrated delivery networks with an eye towards outcomes-based pricing arrangements with manufacturers, (eg, the DrugAbacus developed at Memorial Sloan Kettering Cancer Center and frameworks developed by the American Society for Clinical Oncology [ASCO], the National Comprehensive Cancer Network [NCCN], and the Institute for Clinical and Economic Review [ICER]). In the 5 years, we have firmly entered the "value era" in oncology, with VAFs now serving as a mechanism for payers, providers, and healthcare systems to systematically incorporate varying value-based contributors into the discussion when considering expensive therapeutic options.[7]

All too often, however, the value assessment viewpoints and criteria of payers and health systems are misaligned with those of patients and their caregivers. Often, the foremost features and elements of compassionate care are the first to miss the cut of reimbursement. Many VAFs do not include all the benefits that are important to patients. What matters most to a patient with cancer who is going through a complex and intimidating regimen? How can we maximize the patient's quality of life, regardless of the prognosis? How should these value frameworks consider patients' day-to-day concerns and their willingness to make trade-offs? In 2016, through partnership with FasterCures, Avalere developed a Patient-Perspective Value Framework.

> The digital era creates an opportunity to more closely align multistakeholder value with the patient at the center.

Although this value framework was primarily developed by incorporating patient-centered outcomes, preferences, and patient/caregiver costs, even this VAF in its current form falls short of adequately being specific in many key factors of primary interest to patients. This includes ability for adequate and timely reporting of symptoms and outcomes, monitoring and demonstrating laudable adherence, choosing between medication convenience factors (oral versus IV), communicating with their care team, and ultimately capturing their satisfaction for overall care delivered to them.

Undoubtedly, these frameworks will become more sophisticated as payers and policy makers begin integrating them into episodic and global payment models and clinical and reimbursement protocols. It is an ideal time for digital health technologies to assume a value-based role in generating sufficient clinical, real-world evidence demonstrating improved patient care, and quality of life and satisfaction while reducing healthcare costs. This in turn promotes the integration of more patient-centric value metrics into future VAFs.

## "VALUE ERA" + "DIGITAL HEALTH ERA" = THE FUTURE OF PATIENT CARE IN ONCOLOGY

Digital health technologies can fill current gaps in delivering care to oncology patients, constructively disrupting the current health delivery environment while rebalancing the existing oncology VAFs.

An appropriate starting point is to ask how we best take care of patients, adding emphasis on the patient experience — what they go through, how they feel, and how they live when they are not in the clinic. Cancer patients spend the vast majority of their time outside the clinic; this is where digital health can be impactful in amplifying the patient voice, providing the care team visibility into the patient experience and incorporating it into routine care.

Recent studies have demonstrated the survival benefits of recording patient-reported outcomes (PROs). Delivering these insights back to care teams in a timely manner enables precision intervention. One landmark study by Basch, et al showed how electronic data from a questionnaire of 12 common symptoms when transmitted back to the care team enabled timely management and augmented overall survival. Closer management and coordination reduced the frequency of emergency department (ED) visits and hospital admissions for patients and health systems. More importantly, it reduced the symptom burden between office visits of patients and facilitated increased regimen completion. This intervention led to improvements in overall quality of life, fewer ED visits, and a greater than 5-month survival benefit.[8]

Only through the recent arrival of digital health technologies has it become possible to transmit near real-time PROs, combined with objective data on medication-taking behaviors. With the advent of digital medicines (medications with sensors), such seemingly impossible real-world data that records chemotherapy tolerability and adherence is becoming a reality. Now the objective reliability of IV infusion therapy can be added to the convenience of oral medicines. Objective data is provided by (vs) digital medicines to the patient's mobile app. From there, with patient permission, the data is sent on to their clinicians. With the use of digital medicines, this closed-loop feedback of impatient therapy administration can now be replicated in ambulatory settings. Through enhanced "completion of therapy," patient quality of life and reduced symptom burden can be maximized, ideally leading to increased survival rates. Importantly, the care teams' juggling act (eg, symptom management,

dose titration, adherence verification, and cycle documentation) can be grounded in consistent, objective data. This facilitates greater adherence to therapy and further attention to meaningful PROs, enhancing therapy completion.

The optimal digital health solutions should ultimately seek to bridge the current patient-clinician communication gaps. Achieving this reduces unnecessary clinical visits, particularly to the ED and hospitals. Likewise, optimizing the proportion of doses ingested reduces medication wastage and unnecessary overtreatment. As such, the value for both the patients and healthcare stakeholders (eg, clinicians, caregivers, payers) can be simultaneously captured and rebalanced in favor of treatments with demonstrable real-world effectiveness. The *digital era* creates an opportunity to more closely align multistakeholder values with the patient at the center. This in turn helps future value assessment frameworks incorporate the latest elements of precision care delivery for the *value era* in oncology.

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# Estimands—What Do They Mean for Health Technology Assessment?

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## KEY POINTS

An estimand aims to clarify whether a clinical trial is actually measuring what we think/hope it is measuring.

While the ICH E9 revision focuses mainly on pre-approval activities and stakeholders, estimands will also play an important role in late phase.

Despite the current lack of clarity surrounding implementation, the HEOR community should welcome the revision.

Estimands are coming! The upcoming revision of the International Conference on Harmonisation (ICH)'s E9 "Statistical Principles for Clinical Trials" places greater emphasis on the thorny issue of whether what is actually being estimated in a clinical trial reflects what was intended when the trial was designed. This increased emphasis is framed around the concept of the "estimand"—a term that this ICH revision introduces. Estimands will have a considerable impact upon the design, conduct, and analysis of clinical trials, especially those destined for regulatory submission. This as a very good thing—more thought is definitely needed to ensure that clinical trials do a better job of answering the scientific questions they seek to address.

> How will the practicalities surrounding the implementation of ICH E9 be addressed? And, more importantly, who's going to do it?

This brings us to our first, albeit somewhat pedantic criticism. Although we applaud the effort, we are less convinced by the confusing attempt at branding. Could the E9(R1) authors really not have thought of a better name than "estimands?" Or at least one that sounds a little less like other related and commonly used terms, such as "estimator" and "estimate?"

Putting any naming criticisms aside, it's entirely conceivable that estimands will play an even greater role in the later phases of clinical development. Indeed, the role of the estimand has not escaped ISPOR's attention. A formal response to EMA's request for comments on the addendum has been made by ISPOR this year, following a recent survey of their members. While the ISPOR reviewers gave generally positive feedback, they quite rightly highlighted the limited coverage of the impact of estimands upon post-regulatory approval activities and related stakeholders. Clearly, observational studies and pragmatic trials suffer more acutely from the types of problems that this ICH revision seeks to address. The occurrence of intercurrent events (such as patient dropout, treatment switching, and rescue medication) complicate the estimation of treatment differences in most clinical trials, and especially in low-interventional and real-world studies. These issues convolute, in often subtle and unquantifiable ways, the interpretation of the treatment difference being estimated. The need for a solution that the estimand aims to provide is arguably even more urgent in the health technology assessment (HTA) environment than that in the pre-approval setting.

HTA professionals have a certain luxury in relation to this revision—they will probably be able to observe how the use of estimands evolves in early development before being forced to consider it in their plans. Indeed, they might be well-advised not to rush their adoption. Embedding estimands as part of an addendum to ICH E9 was probably the one way to ensure that it won't make any 2018 readers' choice shortlist. Containing this very critical, cross-functional issue within a statistically focused ICH guidance document could well lead to a slow and tortuous adoption. Given its isolated positioning with the overall guidance, non-statisticians will no doubt interpret estimands as a "problem" that the study statistician alone needs to solve.

How will the practicalities surrounding the implementation of ICH E9 be addressed? And, more importantly, who's going to do it? If estimands end up being discussed in just the statistical sections of a study protocol, then there are no prizes for guessing who's going to end up writing them. Non-statisticians won't exactly be eager to start tackling the subtleties between study objectives, endpoints, outcomes, variables, estimates, estimators, and [deep breath] estimands. In this we see a danger of the ICH revision not being properly addressed in many relevant sections of a study protocol, but rather abandoned in the "statistical section." Guidance on these sorts of protocol-development issues is urgently required.

It is perhaps easy to be overly critical here, and there are already plans afoot to revise other ICH guidance (E8 springs to mind) in line with E9, such that awareness spreads to functions other than statistics. Updates of other ICH guidance should make the process of incorporating estimands throughout a protocol clearer. We therefore advise patience; the understanding, appreciation, and use of estimands will surely improve.

HTA professionals need not necessarily fear the rise of the estimand. There is considerable overlap between this and other concepts often employed by the post-regulatory approval, real-world data environment. PICOT springs to mind, which specifically aims to address important issues such as the population and outcome of interest, among other estimand-related topics. The PICOT "branding" is arguably better too.

In some respects, it's a shame this E9 revision is even needed. Indeed, one might be forgiven for assuming that treatment estimation challenges would already have been given their due attention, but sadly ICH must feel (quite rightly) that the industry needs a considerable push in the right direction.

Estimands are coming and with a potentially huge impact in both pre- and post-approval settings. Those of you with a penchant for wordplay might have recognized that an anagram of "ESTIMAND" is "A MINDSET" — something which we'll soon all need to adopt.

*Additional Information:*

*For more information on the ISPOR Health Technology Assessment Special Interest Group, go to https://www.ispor.org/sigs/HTA.asp*

# How Health State Utilities Used in Cost-Effectiveness Models Are Currently Identified, Reviewed, and Reported

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## KEY POINTS

The reporting standards describing the sources, actual values, justification for final choice, and application of health state utilities in cost-effectiveness models are currently poor.

The selection of health state utilities used are rarely informed by literature reviews, and fundamental details such as the preference-based measure used, the sample size, and details of patients' health condition are rarely reported.

Poor practice has been the norm rather than the exception, but authors of an ISPOR Task Force Report are hopeful that their new checklist and associated recommendations will help lead a rapid change in practice.

Health state utilities (HSU) are used to generate quality-adjusted life years (QALY) in cost-effectiveness models to inform budgetary policy decisions in healthcare. It is recommended that all parameters in these models are informed by a systematic review of the literature. For HSUs in particular, while these may not need to be totally exhaustive, the aim of searches informing the review should be "to identify the breadth of information needs relevant to a model and sufficient information such that efforts to identify further evidence would add nothing to the analysis."[1,2] One rationale behind this recommendation is to enable reviewers to determine that evidence has not been identified "serendipitously, opportunistically or preferentially."[3]

> It has been shown that differences in the preference-based weights, the baseline values, and the methods used to combine evidence, can influence the results generated to such an extent that they could potentially influence a policy decision.

However, a quick Google search quickly identified articles demonstrating this recommendation is not followed by either authors or peer reviewers of articles submitted to academic journals.[4] Indeed, the descriptions of the HSUs used are so lax as to question the validity of some of the evidence, and a skeptical reimbursement agency might be concerned about the motivation of the authors. For example, the entire description of the HSUs used in one model published in 2012 is summarized by: "The utility estimates for each health state were based on a prior estimate." There is no other text in this peer-reviewed article relating to HSUs other than a value and an additional reference in a table. On checking, we discovered there are no HSUs in the source cited within the text. The second source (published in 2007) provided in the table cited a publication from 1997 for the HSUs. After locating this third article, we discovered the evidence used was elicited directly from a small group of patients using standard gamble techniques. So an article published in 2012 incorrectly cited one source, inferring the evidence was relatively recent through citing a 2007 publication, but actually used evidence elicited before 1997, derived from methods that do not meet reference case for many agencies.

In an article published in 2011, the full description of the evidence used for HSUs stated, "Data on utilities for specific health states were identified using the Cost-Effectiveness Analysis Registry as well as Medline searches." It took 3 iterations to identify the original source for some of the HSUs, the earliest of these dated 1986 (the majority were published in early 1990s). Many of the reported HSUs do not match those in either the cited sources or the original source studies. The method or measure used to obtain the HSUs differs for each of the 5 health states in the model. Three different studies provide HSUs elicited directly from patients using time trade-off. The measures used to get HSUs for the remaining 2 health states are less clear: the cited/original sources have a) evidence collected using 6 different generic preference-based measures but it is unclear which actual HSUs were used because the values in the article do not match those in the source; and b) evidence collected using the Quality of Well-Being scale and/or the SF-36. Again, it is unclear which evidence was used because the original source provides data for health dimensions, not the required HSUs. So again, an article published in 2011 cited inappropriate sources and used evidence collected over 2 decades earlier. It also did not provide all the values used and is presenting evidence collected using a variety of methods and measures within the same model.

A third article (published in 2010) provides cynical readers additional food for thought. The authors reported, "All patients in the >

model had an assigned initial baseline utility, which was updated as the patient ages based on values reported in the literature, Utility weights for each model event were based on consensus estimates reported in the literature, as noted in Table 2." The authors did not provide the actual HSUs used for the baseline, nor did they state which method or measure was used to obtain these. As in the previous example, the cited source provides evidence collected from 6 different generic preference-based measures, thus it is not possible to determine what data were used. For the 5 different "model events," either the HSUs reported were not in the referenced source or they did not match the values in the original sources. For example, the authors reported decrements of 0.037 and 0.0175 for coronary artery bypass graft and percutaneous transluminal coronary angioplasty, respectively, while the original sources reported these were 0.042 and 0.059, respectively. Surprisingly, the authors reported an HSU of 0.5 for the "death" health state. Death is an absorbing health state and one wonders if the analyst allows dead people to accumulate 0.5 QALYs just in the first year, or every year over the full lifetime horizon modelled. Finally, they state "multiplicative utility calculations were performed," whereby the 'joint' utility value was the product of the individual utility values." It isn't obvious how this is physically modelled, given that their reported values are disutilites. So this article cited inappropriate sources, did not report all the data used, "tweaked" the evidence with no explanation, and were extremely vague regarding how the HSUs are used to calculate the QALYs.

The above study was funded by industry but the following example demonstrates that poor practice is not limited to that community. Authors of a recent UK National Clinical Guideline made no attempt to identify the most relevant or appropriate evidence simply stating, "We adopted the same utility multipliers for health states as HTA X, 2007 (these were determined following a systematic review), supplemented with values used by Y for states not included in HTA X's model."[5] Whilst acknowledging "they are sourced from multiple different studies, conducted in different settings, and which elicited quality of life preferences using different methods. As a result they may not be entirely consistent." What the authors don't clarify is that several of the values used were estimated or adjusted in some way by authors of the cited article and thus do not match the source values.

The following example illustrates the huge variations in HSUs chosen when evidence is selected in an ad hoc manner, and the difference in methods used when applying these in models. Looking at evidence in a review comparing the HSUs from 6 articles (published in either 2010 or 2011) reporting cost-effectiveness analyses of prophylactic interventions for cardiovascular disease; 4 use constant HSUs (range 0.76 to 1) for the baseline (ie, patients at risk of a cardiovascular event with no history of cardiovascular disease) while 2 use age-adjusted values. The absolute decrements for a coronary event range from -0.05 to -0.24, and for stroke range from -0.11 to -0.5. One of the studies reported that HSUs are multiplied together whilst all the others use absolute decrements. One applied the event decrement for just one year and then allowed the utility to revert to the baseline. Another calculated HSUs by weighting values with the numbers of events observed in a specific trial, then applying zero QALYs after the event. Given the proximity of the publication dates and the similarities in interventions and target populations under appraisal, one might justifiably expect that the HSUs and methods used to apply these would be more consistent across these articles.
We know that the measures and methods used to obtain HSUs make a difference to the values obtained. First, there are substantial differences in the possible HSUs when comparing across the ranges in HSUs obtained from generic preference-based measures. For example, the HUI ranges from -0.36 to 1, while the SF-6D ranges from 0.30 to 1.[6] It has been shown that this can result in different HSUs for the same health condition even when collected from the same people at the same point in time. [7] Second, even the same measure can produce different HSUs from the same sample depending on the individual country preferences weights that are applied to the initial responses to the questionnaire.[8] We also know from multiple sources providing population norms that on average HSUs decline by age irrespective of setting or measure used[9-10], and the mean is never equal to full health irrespective of age or gender.[11] It has also been shown that differences in the preference-based weights, the baseline values, and the methods used to combine evidence, can influence the results generated to such an extent that they could potentially influence a policy decision.[12-13]

A recent review of the literature illustrates that the examples above are not outliers. Looking at recent articles exploring the cost-effectiveness of pharmaceutical interventions in cardiovascular disease, the authors identified 24 studies published since 2015. Of these, just one reported they undertook a literature review to inform the HSUs and just 6 correctly referenced the original sources for all the HSUs. None of the studies provided basic details of the studies or samples used to obtain the HSUs such as the sample size, details of the health condition, timing of data collection, etc. Half did not report which measure was used to collect any of the HSUs, 6 of the studies used HSUs from at least 3 different measures, and just 2 used HSUs from the same measure for all health states in the model. There was substantial variation in the HSUs used for the baselines and large discrepancies in the values used for the individual health states.

This reinforces the importance and need for robust and transparent methods to justify the evidence selection and choice. An ISPOR Task Force has been reviewing the issues encountered when identifying, selecting, and using HSUs in cost-effectiveness models and is expected to publish a report later this year. A checklist is provided for critiquing the appropriateness of the HSU evidence — including search strategies, the review process, and the selection of HSUs used — and the methods that are employed when applying the evidence in the cost-effectiveness model.

The Task Force report is not simply designed to help those wishing to undertake a systematic review of utilities for a cost-effectiveness model. Instead, we think that this report and the SPRUCE checklist also should be used as a tool by reviewers of manuscripts and reports of modelling work to determine their suitability or validity. The Task Force recommends that HTA bodies, academic review groups, model developers, and journal reviewers use the recommendations from the work and the checklist to improve the quality of models. It is clear how important utilities can be to inform cost-effectiveness models, and the examples above indicate the manner in which they are being sourced in published studies. We hope that the Task Force report will help to lead a change in practice among modellers regarding the manner in which this information is gathered and used.

Peer reviewers should not allow cost-effectiveness modellers to assign HSUs to the "caveat" box any longer; they have got away with this for far too long. The poor standards that are currently accepted as the norm do have implications. They undermine the rational for using the cost per QALY which is to facilitate comparison of interventions across diseases and treatments. One wonders if this practice would be so readily accepted if the evidence was describing the clinical effectiveness of an intervention.

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*Additional Information:*

*The preceeding article is based on a workshop given at ISPOR 2018.*

*To view this presentation, go to https://www.ispor.org/docs/default-source/presentations/1386.pdf?sfvrsn=bb54e551_1.*

*For more information on the Health State Utility Estimates in Cost-Effectiveness Models Task Force, go to: https://www.ispor.org/member-groups/task-forces/health-state-utility-estimates-in-cost-effectiveness-models.*

# Q&A

## Blockchain and Electronic Medical Records: An Interview With Renata Nunes Aranha and Leticia Lazaridis Goldberg

*Value & Outcomes Spotlight's* editorial board member, Marisa Santos, had the opportunity to sit down with Renata Nunes Aranha, cofounder of Rede Entropia, a venture and artificial intelligence (AI) and blockchain lab, and Leticia Lazaridis Goldberg, head of Entropia HealthTech and CEO of Eversafe, to discuss the latest in cutting-edge developments in blockchain and its relation to electronic medical records (EMR). Renata coordinated the creation of the Medical Graduation Project at Pontifical Catholic University in Brazil and worked on the implementation of innovative projects in various universities. Leticia possesses a unique perspective on the healthcare space, which has enabled her to work in a variety of cross-functional positions within the sector.

Renata Nunes Aranha

***Value & Outcomes Spotlight:*** **Blockchain is considered one of the most important inventions in recent years, created for someone known by a pseudonym, Satoshi Nakamoto. But most health professionals can only associate it with bitcoins (cryptocurrency). Could you explain what blockchain is?**

***Renata Nunes Aranha and Leticia Lazaridis Goldberg:*** Blockchain is a Distributed Ledger technology that permanently records transactions in chronological order across a decentralized network of public or private computers. The technology prevents the record from being changed retroactively and allows the community to verify the authenticity of transactions.

Leticia Lazaridis Goldberg

The technology is based on 4 basic pillars: (1) **Distributed ledger**: each participant on a blockchain network has access to the complete information; (2) **Decentralized**: no single entity controls the information; participants validate the records of its transaction partners; (3) **Smart contracts**: a contract that determines the rules of operation of the transactions; and (4) **Asymmetric cryptography**: use of public and private key cryptography and cryptographic hash functions.

**How can it be applied in healthcare?**

Some examples of uses of blockchain technology that can help transform the healthcare industry include personal health record management, healthcare analytics, security and interoperability of Internet of Things and medical devices, supply chain management, and patient recruitment for clinical trials, among others.

At Entropia Health, we are working on Eversafe, a blockchain application that allows us to connect the silos of previously fragmented healthcare data, realign the incentives of diverse stakeholders, and give individuals more governance over their medical data. Individual users of health systems are at the center of EverSafe and will be empowered to access, manage, and share their health data through our platform.

> Our vision is to put individuals at the center of the platform and build a complete picture of one's health. By bringing data together, tremendous wealth is generated that should be distributed to all stakeholders.

**What are the advantages for patients and managers? What are the possible applications for clinical research and will it be more expensive?**

Because of the immutable characteristics of the technology, blockchain can better ensure the resilience, provenance, traceability, and management of healthcare data. Patient recruitment for clinical trials is an expensive, time-consuming stage. Blockchain can expedite patient identification and matching. Additionally, the technology can validate data, incentivize participation, and allow for consent through smart-contracts.

**What are the risks and disadvantages? Can we have confidentiality issues? Could you speak about the global blockchain market and real experiences with blockchain in healthcare?**

We know the technology is useful to track how data have changed over time, but do not have benefits that are superior to conventional tools. This means that the risk of people altering essential health data decreases. However, there is a chance that more people may be able to access data given the decentralized nature of the blockchain. In the healthcare sector, many opportunities exist for using blockchain technology, and a few projects are already underway. Some examples are: CareChain, a European consortium to establish a public-permissioned infrastructure to manage health data owned and controlled by no one except the rightful owners (ie, the individuals); MedRec, a project designed by MIT, uses Ethereum for patients to control their medical data, including clinical EHR records and data from personal health wearables like Fitbit; Blockpharma is a French start-up focused on solutions to trace drug sales online; and AMCHART, a patient-driven EHR on a hybrid public/private blockchain with AI for analytics and an incentive-driven model for better outcomes.

**How does one know if blockchain should be applied to an organization's projects?**

To determine whether your project may be a strong blockchain use case, you first need to have a deep understanding of the problem you are trying to solve and map the existing solutions that are in place. Then, select the cases that meet the following basic criteria: the problem involves written contracts with multiple parties; the extremely complex processes that maintain a multilevel validation chain; transactions that require traceability; transactions that require unique and non-changeable records; the need to increase or establish trust relationship among members of the business network; the need to track the ownership and control of a physical or virtual asset; or significant manual/human intervention needed for any part of the data or transaction processing.

**Can you highlight some challenges and research needed in the blockchain arena?**

The implementation of a blockchain project requires much coordination with all parties involved. Importantly, because of the novelty of the technology, we need to educate people about the benefits and applications for their businesses. The current operational systems for blockchain applications still pose significant challenges. Some platforms have scalability issues, where others still need more adoption and software stability.

Another challenge is building a team with a decentralized mindset. Most of us were trained on centralized business models, so when it comes to designing a decentralized blockchain business model, we need to pay special attention to participants' incentives and how to generate wealth that can be distributed among the network members. Moreover, software engineers that can work on blockchain projects are hard to find and expensive. In a world of data silos, where companies are treating people's data as their assets, we must challenge this paradigm. Our vision is to put individuals at the center of the platform and build a complete picture of one's health. By bringing data together, tremendous wealth is generated that should be distributed to all stakeholders.

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