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Advancing Healthcare through Innovation and Collaboration

An Interview with Gigi Hirsch, MD

Executive Director, Center for Biomedical Innovation,
Massachusetts Institute of Technology and Director NEWDIGS

NEWDIGS is an exciting and innovative approach to developing solutions for systemwide impediments to biomedical innovation and patient care. The non-competitive, collaborative environment encourages novel and fresh ideas and interactions to truly move the industry forward in positive ways. Evidera is currently participating along with other experts from across the healthcare spectrum in the new Learning Ecosystems Accelerator for Patient-Centered, Sustainable Innovation (LEAPS) project, which is designing and piloting an ecosystem for purpose-driven evidence generation and integration focused on a critical disease area (including both real-world evidence and data from randomized controlled trials).

Dr. Debra Schaumberg, Vice President, Scientific Affairs, Real-World Evidence at Evidera recently sat down with Dr. Hirsch to discuss the NEWDIGS initiative, the LEAPS project, and the hope for transformation of the healthcare ecosystem.

Debra Schaumberg

Please tell our readers a bit about the MIT NEWDIGS consortium.

MIT NEW Drug Development ParadIGmS (NEWDIGS) is an international "think and do tank" dedicated to delivering more value from biomedical innovation faster to patients, in ways that work for all stakeholders. NEWDIGS designs and pilots system-level innovations that are too complex and cross-cutting to be addressed by a single organization or market sector. Its members include global leaders from patient advocacy, payer organizations, biopharmaceutical companies, regulatory agencies, clinical care, academic research, and investment firms.

The LEAPS Project focuses specifically on aspects of a learning healthcare system that improves our ability to get the right treatment to the right patient at the right time – that is, optimization of therapeutic regimens. Within this context, there are a number of relevant challenges to attaining a true learning healthcare system. In laying the groundwork for the LEAPS Project, we think of these challenges falling broadly into three, inter-related categories associated with real-world evidence and learning.

1. **Planning.** Traditionally in biomedical innovation, evidence-based learning stops at the point of regulatory approval. Consequently, most of the evidence needed for real-world decision making by patients, providers, and payers is missing. A true learning health system requires that evidence essential for real-world decision making is prospectively planned with input from all key stakeholders in order to be fit-for-purpose to improve decisions and patient outcomes.

2. **Production.** The current approach to producing real-world evidence is fragmented, inefficient, and extremely costly. Applying traditional approaches to fill current real-world knowledge gaps that undermine our ability to optimize therapeutic regimens – i.e., one study/drug/stakeholder at a time - will simply not get us where we need to go.

3. **Use.** A true learning healthcare system would fully leverage evidence produced by making it available in timely ways to those making clinical decisions, updating policy and practice standards, and informing next generation biomedical innovation priorities and strategies.

Designing and implementing a scalable, sustainable learning system must address all three of these domains through the coordinated evolution of policies, processes, and technologies – and, most importantly, the associated alignment of incentives around patient-centered learning.

Evidera is collaborating with NEWDIGS on the LEAPS project. Could you explain to our readers more about this initiative and its goals and methods?

The LEAPS Project of the MIT NEWDIGS consortium focuses on transforming how key stakeholders in a disease ecosystem (i.e., patients, providers, payers, regulators, and developers) work together in the planning, production, and use of real-world evidence in order to more reliably optimize regimens of therapeutics.

Success in the LEAPS pilot will require that stakeholders collaborate to create new infrastructures - evidence generation platforms - designed for patient-level impact, scale, and sustainability. Collaborators will create a "Learning Engine" for a target disease that has significant implications for value creation and capture by all parties in two key domains: 1) the translation of data into knowledge that improves decision making related to therapeutic development, access, and use; and, 2) the impact of therapeutics on clinical outcomes.

Success metrics include both improved patient outcomes, as well as reduced waste and inefficiency across the system. LEAPS collaborators are designing a model system for rheumatoid arthritis (RA) for a pilot in Massachusetts (MA), the "RA MA pilot," and will extract generalizable design principles to inform related efforts in other diseases and geographies. The RA MA pilot is expected to launch in 2020.

Dr. Hirsch is the Executive Director of the MIT Center for Biomedical Innovation (CBI), which focuses on improving global health by overcoming challenges to the development, diffusion, and adoption of biomedical innovations.

Her current efforts at CBI center on leading the New Drug Development Paradigms initiative (NEWDIGS), a program that is re-engineering pharmaceutical innovation to deliver new, better, affordable therapeutics to the right patients, faster. Within the broad strategic framework of "Adaptive Biomedical Innovation (ABI)," NEWDIGS' flagship project focused on aligning stakeholders around more adaptive, patient-centered approaches to the management of risk and uncertainty across the life span of new medicines. This project helped inspire the Adaptive Pathways pilot program launched by the European Medicines Agency (EMA) in March 2014.

Under Dr. Hirsch's leadership, NEWDIGS continues to channel multi-stakeholder thought leadership to advance other critical enablers of ABI such as structured evidence planning and production across the product lifecycle; efficacy-to-effectiveness (E2E) strategies, tools and systems; precision financing models for curative therapies; and, simulation methods/tools for collaborative innovation.

Dr. Hirsch has held a number of leadership roles that leverage her broad clinical background (internal medicine, emergency medicine, and psychiatry) along with her passion for innovation, entrepreneurship, and improving patient outcomes. Prior to joining CBI, she served as Director of Academic and Professional Relations at Millennium Pharmaceuticals and was founder and CEO of a boutique entrepreneurial venture (MD IntelliNet), funded by Boston's Beth Israel Hospital. She has held faculty appointments at the medical schools of Harvard, Brown, and Tufts after receiving her medical degree at the University of Cincinnati.

Why is it important to engage multiple stakeholders in this effort?

LEAPS builds on NEWDIGS' guiding principles for collaborative system design where success requires a multi-stakeholder view of the following dimensions:

- **Identifying the problem/need** - what is working and not working in the current target area of the system, from each stakeholder's perspective
- **Defining the design "space"** - given the highly regulated nature of this industry, identify which aspects of the system that may be contributing to the problem(s) are fixed versus flexible, and consequently, which ones are approachable for innovative solutions

- **Understanding success drivers** - including value and risk drivers for each stakeholder, and critical inter-dependencies across stakeholder silos in the target area of system improvement

Effective and sustainable success in system level transformation requires that all stakeholders be actively engaged from the outset of any design initiative within NEWDIGS.

How hard is it to get stakeholders to start to "think differently"?

One of the greatest challenges, and most warmly embraced aspect of collaboration in LEAPS, is the opportunity to work together with other stakeholders in ways that are simply not possible in one's day job. Collaborators often comment that they are smarter after a LEAPS Design Lab than when they came in.

Examples of guiding principles in NEWDIGS, and in LEAPS, designed to foster innovative thinking include:

- ***Patient-centered innovation cannot be achieved one silo at a time.*** Rather, it requires stakeholders to work together in fundamentally different ways to optimize tradeoffs and "collective impact" for patients.
- ***Decisions made in one silo have implications for other silos.*** Patient-centered decision-making requires the explicit exploration of tradeoffs, and collaborative approaches to reducing risk or uncertainty can change decisions, actions, and outcomes.
- ***Science evolves from left to right (i.e., from discovery to development to delivery). Evidence, on the other hand, should be planned from right to left (i.e., informed by downstream decision-makers).*** Value (as defined by patients, clinicians, and payers) must be considered earlier in drug development.

2019 is the 10th anniversary of the MIT NEWDIGS initiative, and much of our success is driven by the collaborative design tools and methods, and our safe haven, the pre-competitive Design Lab environment that we have developed to support "thinking differently" in ways that drive timely, real-world impact. We have a track record of advancing from concept to real-world pilot within three years, which helps collaborators trust in the process we use to think outside of one's silo.

What is your (LEAPS) perspective on closing the gap between how medical products are developed (e.g., the randomized controlled trial infrastructure that has evolved to address regulatory requirements) and the evidence needed to guide real-world use of the products (e.g., RWE)?

Closing the knowledge gaps between the *development* and the *real-world use* of biomedical innovations is critical to the future of biomedical innovation and is at the heart of the NEWDIGS LEAPS project.

As value-based healthcare gains traction, the future of biomedical innovation is at risk, as illustrated by the current state of RA in which massive, complex knowledge gaps exist that undermine our ability to optimize treatment regimens. The future depends on answering the questions underlying these knowledge gaps, yet the current approach to biomedical evidence generation is expensive, lengthy, laborious, and narrowly focused, i.e., "one question, one drug, one stakeholder." Biomedical innovation cannot succeed without transforming evidence generation such that we are able to answer more questions, better, at scale, and at lower cost.

The LEAPS vision builds on the recognition that we simply cannot get where we need to go using traditional approaches to evidence generation. As detailed in the earlier question about the challenges in building this new ecosystem, we need to fundamentally transform how we plan, produce, and use real-world evidence to ensure that biomedical innovation, and value-based healthcare, are both successful and sustainable.

What role do you envision for the evolution of a real-world evidence infrastructure to enable the development of a learning ecosystem?

As noted earlier, our ability to optimize therapeutic regimens is undermined by current gaps in real-world knowledge that are massive and complex, and current approaches to evidence production are too fragmented, inefficient, and costly to successfully meet the challenge.

Central to the LEAPS approach to addressing this challenge is the use of *platform strategies* to develop better real-world evidence, faster, and at lower cost. Platform strategies have driven the advancement of the high-tech industry but have only recently been explored for evidence production in healthcare, beginning with adaptive platform trials of investigational drugs to advance precision medicine in oncology.[1] Recent real-world evidence generation platforms have leveraged learnings from these innovative clinical trial designs and integrated them with a novel approach to point-of-care studies, embedded into clinical practice.[2] This concept is illustrated in Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP), which is evaluating multiple domains for treatment of community-acquired pneumonia across multiple intensive care units (ICUs) in Australia, New Zealand, and Europe. The REMAP-CAP platform is embedded within the electronic health record (EHR) of participating institutions and is designed to simultaneously address multiple questions regarding treatment of community-acquired pneumonia, such as the best way to manage the ventilator, the best antibiotics and fluids, and whether steroids should be administered, etc. Ongoing evaluation of patient outcomes informs changes in platform design elements as data accumulates allowing clinicians to respond more quickly to both successful and unsuccessful therapies. Thus, as the platform generates

evidence, treatment improves, and so does the chance of patients receiving the most effective treatment for their situation.[3]

Using RA as a model, LEAPS is harnessing lessons learned from these pioneering endeavors to target the next frontier in biomedical evidence generation platforms: applying platform strategies to the real-world treatment of chronic diseases in ambulatory settings. The LEAPS Learning Engine will consist of multiple coordinated platforms, each tailored to address a specific type of knowledge gap in terms of data collection, analysis methods, and data sources. For example, the LEAPS RA MA pilot will initially include two separate, but coordinated, platforms. The *Real World Discovery Platform* (RWDP) will apply artificial intelligence and machine learning to a diverse, distributed set of data sources to identify and replicate predictive markers. In contrast, the *Adaptive Point of Care Platform* will be embedded in decision making at the point of care and will employ adaptive methods to continuously learn and improve treatment selection for a given patient.

How are patients informing this transformation?

Designing and implementing an effective learning ecosystem requires the active participation of patients and patient advocacy groups. Patient engagement in LEAPS goes far beyond simply inviting patients to participate in our Design Lab events and extends to their involvement in the work of our multi-stakeholder design teams. Patients provide valuable input on understanding unmet needs, designing and vetting emerging solution concepts, and planning specific aspects of the blueprint for our RA MA pilot. We are particularly excited to have the opportunity to work with the Arthritis Foundation at both the national and state (Massachusetts) level in LEAPS.

Are we missing any critical elements? What skill sets are needed or need to be further developed within the healthcare industry writ large?

In many ways, LEAPS is about shifting our focus in biopharma and healthcare from bigger data to smarter evidence. As this transition unfolds, it will be critically important for organizations that have historically collected data from their daily work to enhance their understanding of how to more fully exploit the value of the data for their organizations and for others in the ecosystem. This will require a deep understanding of the context of this data, and how to leverage it to improve decision making within the organization as well as more broadly within the ecosystem. Advanced analytics and research methods will certainly be an important part of this evolution, but so too will strategic systems thinking, science-driven policy making, and adaptive organizational leadership – both within individual firms as well as within pre-competitive, public-private collaboration environments.

What's the "downstream" vision for LEAPS? In other words, in the land of LEAPS, how do we generate and use evidence?

Learning in the "Land of LEAPS" will be fueled by harnessing the data that is generated as a byproduct of the daily lives of stakeholders across the value chain, from bench to bedside to home to bench. Platform strategies will leverage targeted access to associated distributed data sources, and appropriate analytic methods, to produce better evidence faster and at lower cost. Wherever possible, data access and analytics will be embedded in work flow processes to enhance scalability and sustainability. Dissemination of evidence will be optimized for timely delivery to decision makers at the point of care, and in meaningful ways for incorporation into processes by which policy and practice standards are updated for key stakeholder groups.

For example, the LEAPS RWDP is now being designed to enable hypothesis generation related to identifying subpopulations that are "super-responders" or "non-responders" to specific classes of RA therapeutics. Once validated, evidence emerging from the RWDP will ideally impact clinical practice, payer step therapy policies, and potentially future clinical guidelines. The ability to identify non-responders to a TNF inhibitor therapy, for example, would more rapidly allow patients to move from a non-effective therapy to one that could potentially be more effective for them, thus providing earlier symptom relief and preventing further disease progression. Evidence generated from the RWDP would also likely impact decisions within biopharma companies, with the potential to influence product development strategy and clinical trial designs. ■

For more information on NEWDIGS and LEAPS, visit https://newdigs.mit.edu/.

REFERENCES

1. Barker AD, Sigman CC, Kelloff GJ, Hylton NM, Berry DA, Esserman LJ. I-SPY 2: An Adaptive Breast Cancer Trial Design in the Setting of Neoadjuvant Chemotherapy. *Clin Pharmacol Ther.* 2009 July;86(1):97-100. doi: 10.1038/clpt.2009.68. Epub 2009 May 13.
2. Angus D. Fusing Randomized Trials with Big Data: The Key to Self-learning Health Care Systems? *JAMA.* 2015 Aug 25;314(8):767-768. doi: 10.1001/jama.2015.7762.
3. REMAP-CAP: Randomized Embedded Multifactorial Adaptive Platform Trial in Community Acquired Pneumonia. 2016. Available at: https://clinicaltrials.gov/ct2/show/NCT02735707. Accessed May 28, 2019.

The Role of Integrated Scientific Advice for the Early Determination of RWE Requirements in HTA and Payer Assessments

Andrea Schmetz, MBA
Senior Consultant, Market Access Consulting, Evidera

Stephanie Wise, MPharm
Consultant, Market Access Consulting, Evidera

Matthew Bending, PhD
Executive Director of HTA Strategy and UK Practice Lead
Market Access Consulting, Evidera

Patricia Hurley, PhD
Senior Director, Strategic Regulatory Consulting, Evidera

Real-world evidence (RWE) is a ubiquitous conversation topic in discussions on the current health technology assessment (HTA) landscape for biotech and biopharma assets. By now it is widely known that RWE is an unavoidable part of drug development and should be given thorough consideration, ideally early on; a simple online search for "the importance of real-world evidence in HTA" reaps thousands of results. High-quality practice guidelines lead the way to explaining how to develop robust RWE, e.g., through the Innovative Medicines Initiative's (IMI) GetReal project, the International Society for Pharmacoeconomics and Outcomes Research's (ISPOR) RWE task force, and other instructional articles.[1,2] Despite the availability of such guidance, often health technology assessment bodies, payers, and even regulators do not regard submissions of real-world data or evidence as manufacturers hoped they would. The aim of this article is to discuss the current use of real-world data and evidence in HTA and payer appraisals, its potential role in lifecycle management, and how the early dialogue provided by Integrated Scientific Advice (ISA) engagement can be used as a key tool in real-world evidence generation planning.

RWE is defined by the ISPOR task force as being obtained from the process of analyzing real-world data (RWD), which in turn is defined as data gathered outside randomized clinical trials (RCTs), e.g., through routine clinical practice.[1]


Andrea Schmetz


Stephanie Wise


Matthew Bending


Patricia Hurley

The nature of this data implies that it is less controlled and thus more prone to bias than the data obtained from an RCT.[3] As a result, implementation of robust RWE plans can be almost as work-intensive as planning for an RCT, but the return on investment is not always as obvious to manufacturers. RWE planning also requires significant internal collaboration and "buy-in" across teams as it affects, at a minimum, the clinical, regulatory, HEOR, and market access functions. In the light of this effort, is developing RWE worth the effort?

The impact of RWE in HTA decision making as of today has been explored by multiple stakeholders and interested parties, and results show a clear trend towards more use and impact of real-world evidence in HTA decision making, however, they also outline apparent limitations.[4,5]

- A conference presentation from 2018 outlines the use and impact of RWE in appraisals by the National Institute for Health and Care Excellence (NICE) in the United Kingdom (UK), the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia, the Haute Autorité de Santé (HAS) in France, and the pan-Canadian Oncology Drug Review (pCODR) in Canada in non-small cell lung carcinoma (NSCLC) drugs, where the authors found that RWE was used as supportive evidence for efficacy in a majority of NICE, PBAC, and pCODR appraisals.[5]
- A further research article shows citation of real-world prevalence data in a majority of melanoma drug appraisals and just under half of the 52 reviewed appraisals utilized RWE effectiveness data.[6]
- A study from the London School of Economics shows that RWE is being used mainly in accelerated access by regulators and in re-assessment by HTA bodies.[7]

While these delineate a clear place for RWE in HTA and regulatory decision making today, it can be seen that currently RWE mainly finds use in cost-effectiveness markets. Furthermore, it emerged that the HTA policies within these cost-effectiveness markets are most favorable regarding the use of RWE in evaluations. Nonetheless, most countries' policies clearly state that most weight in decision making is to be given to RCT data.[8]

An interesting observation that emerged during this review was that markets that do not utilize cost-effectiveness analyses in their HTA appraisal procedures also do not seem to utilize RWE for decision making to a large extent. This observation might merit further investigation, as it might suggest that markets not using cost-effectiveness data are still establishing appraisal processes for RWE, creating ambiguity but also opportunity for manufacturers when developing RWE strategies for the markets with larger potential sales volume.

Part of the reason for not using RWE might be the lack of perceived rigor required from evidence as outlined in the law or data protection requirements, as is the case in Germany.[9] However, given the challenges brought by new medicines with long-term effects, such as CAR-T and other gene therapies, those markets currently not using cost-effectiveness data and RWE may need to start considering RWE more in their drug appraisals.

It is, by now, commonly known that healthcare systems are under increasing pressure from innovative, long-term effectiveness therapies that are expensive and come with much uncertainty in terms of their long-term impact.[10,11] As a response, many stakeholders across healthcare systems are starting to look at lifecycle management of drugs. For example, EUnetHTA is dedicating a whole workstream in a Joint Action to lifecycle management, implying a continuous need for data on every asset launched.[12]

Lifecycle management of drugs that incorporates the use of RWE is an increasingly discussed topic as well; large conferences, including the 2019 HTAi conference that Evidera staff attended, gave this topic key importance.[13] A main example cited during the conference was CAR T-cell therapies, where long-term evidence and RWE that have emerged since launch suggest that CAR-T may not be as effective in the long term as initially hoped or projected.[14] Similar results may become reality with regards to other gene therapies in light of the waning effect over time. This constitutes a "perfect storm" for healthcare systems with robust pipelines of promising technologies, with increased demand for early and equitable access likely resulting in a deepening of the affordability crisis. Two key areas of focus in lifecycle management are suggested to address this:

- Removal of low-value technology
- The shift of pricing, reimbursement, and market access (PRMA) decision making to a proactive approach throughout the lifecycle

The UK health system, including NHS England and the NHS Clinical Commissioners (NHSCC) joint working group, represents an example of a healthcare system acting to remove low-value technology. Following a national consultation in 2017, guidance listing 18 items which should no longer be routinely prescribed in primary care was published; this list was updated in 2019 with updates and additions, clearly showing that products are actively being managed off care pathways.[15] Similarly, Germany has just ratified the GSAV (Gesetz für mehr Sicherheit in der Arzneimittelversorgung) law this year, outlining the potential for frequent reassessment throughout products' lifecycles to ensure continued delivery of relative value in a shifting landscape.[16]

As it is evident that RWE is increasingly finding its place and use in HTA appraisals and in market access in general, and healthcare systems will likely see an increasing need for data on pharmacotherapies throughout the product lifecycle, it will be key for manufacturers to establish ways to plan an RWE strategy as early and as efficiently as possible.

Early Engagement with ISA Can Help Shape RWE Plans

Integrated Scientific Advice is a multi-stakeholder advice process that brings together regulatory advice (either with country-level agencies or the European Medicines Agency [EMA]) and HTA advice (either with individual country-level agencies or multi-country collaborations).[17]

Early engagement with ISA is a valuable strategy to refine and evaluate evidence generation plans and align them with regulators' and HTA bodies' needs (See Figure 1). However, a vital question emerges: do regulatory agencies and HTA bodies require a discussion on the plans for developing real-world evidence during scientific advice and to what level are they willing to discuss it?

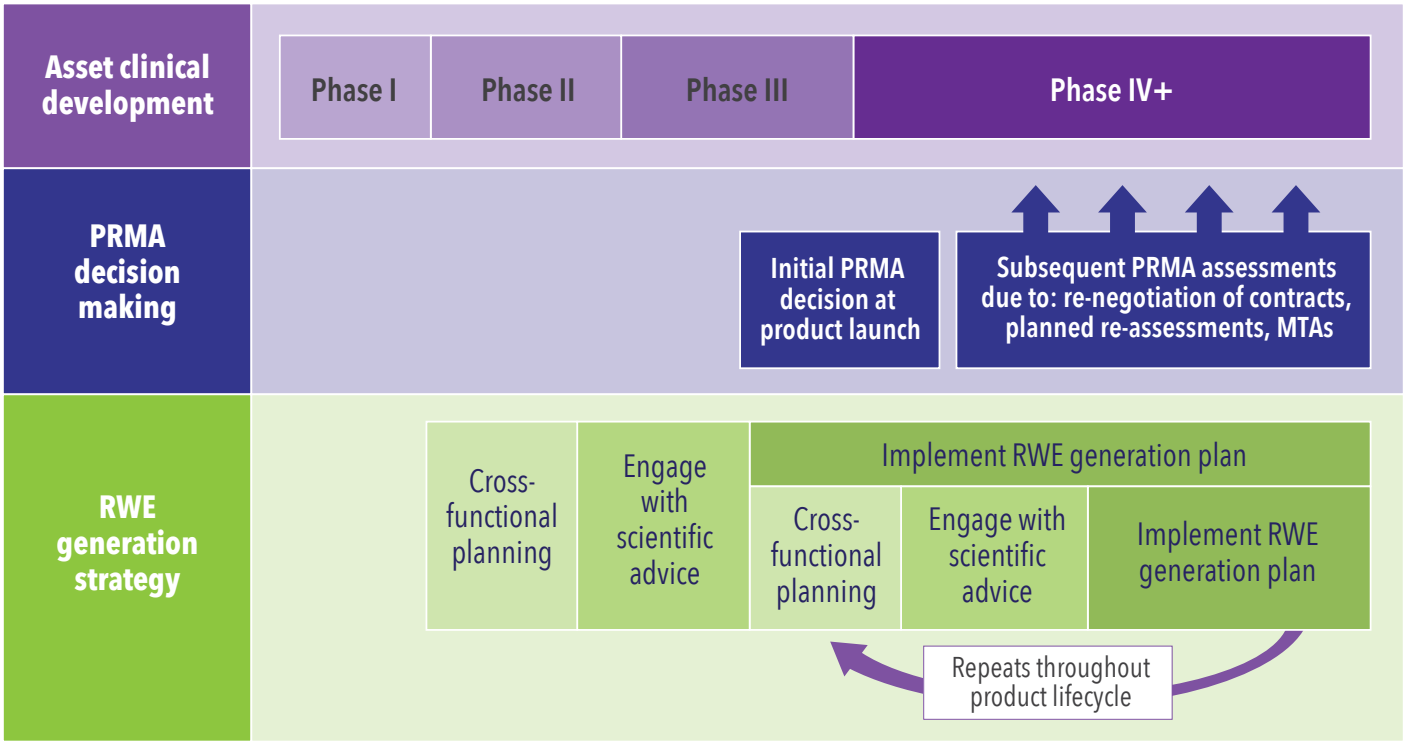
Historically, regulatory agencies have often requested RWD and RWE as mandatory post-launch evidence commitments. They are vital tools to enhance existing safety and efficacy data in the long term to satisfy approval requirements.[18,19] HTA bodies have been traditionally more hesitant to consider RWE and RWD in initial PRMA assessments and thus did not frequently request or consider it. However, contrary to past experience, a new trend seems to be emerging. Evidera has engaged in several early scientific advice and ISA processes in 2018 and 2019 and a shift has been observed in the form of increased requests for and clarifications on RWE and RWD generation. Particularly in the list of issues provided to manufacturers as part of the EU parallel advice program, more requests on RWE planning, e.g., for observational trials and registries, were seen. It seems requests for RWE and the willingness to discuss its inclusion now come equally from HTA bodies and regulators during EMA-HTA Parallel Consultation.

Despite the increasing demand and interest in RWE observed, a key challenge in terms of impact on outcomes remains as was summarized by the former head of NICE scientific advice, Dr. Leeza Osipenko, in an interview with Evidera in 2018: "… unfortunately there is a strong move to start using RWE in place of, rather than in addition to, properly collected and analysed data which are needed to establish relative clinical effectiveness of the intervention. RWE often produces more noise than clinically relevant information."[20]

To avoid having carefully collected RWE or RWD categorized as noise, it will be important for manufacturers to understand requirements in the exact context of their product. General themes that emerged from reviewing scientific advice feedback are in line with good practice guidelines and pointers given by EMA[1,18]; RWE should provide:

- Collection of long-term effectiveness and safety outcomes
- Assurance that manufacturers are prepared to support their therapies throughout the lifecycle
- Preparation by the manufacturer to actively contribute to the development and improvement of overall disease area outcomes
- Generation of data that applies to different healthcare systems and treatment patterns as an acknowledgement

Figure 1. Timeline for Inclusion of RWE Generation Strategy and ISA



that variation inside a randomized clinical trial, and thus local applicability of trial data, is limited

- Demonstration that therapies provide satisfactory relative value in a clinical landscape that is continually evolving, particularly in some disease areas such as cancer

This review also revealed how HTA bodies do not want RWE or RWD to be used, as emphasised by other stakeholder voices, e.g., members of the Cochrane collaboration[21]:

- Evidence collection to circumvent gathering of sufficient clinical trial evidence
- A tool targeted at collection of evidence on a therapy in isolation from the system, e.g., product registry planning versus integration into a disease registry

Global Collaboration is Needed to Improve the Value of RWE

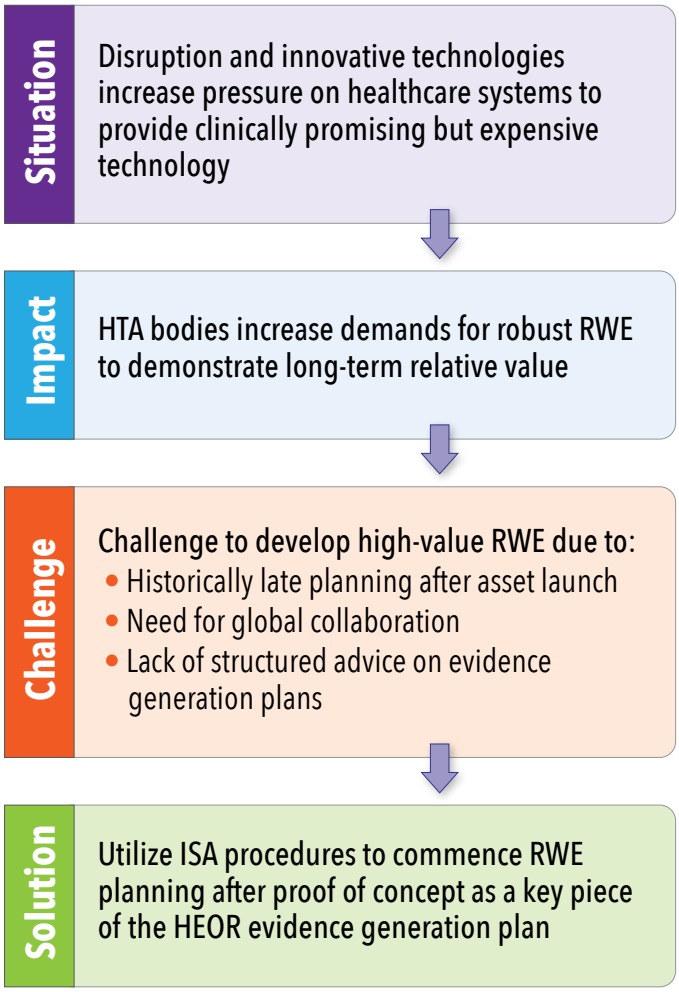
Overall, RWE has established itself as a key part of an asset's evidence generation plan, but it seems that the exact use and design of RWE to make an impact on regulatory and HTA decision making is yet to be defined. In particular, markets not currently using cost-effectiveness data should hold manufacturers' attention, as the role of RWE in these markets seems to be in the early shaping process.

A team at HTAi proposed key focus areas to be developed in order to further the importance and place of RWE in market access, including global collaboration to provide leadership in the form of an accreditation body and establishment of common legal and methodological frameworks.[22] At the HTAi Global Policy Forum conference in January 2019, it could be seen that this work has already begun in the form of EUnetHTA's Work Package 5, titled "Life Cycle Approach to Improve Evidence Generation.[12]" The objective of this work package is to help generate robust evidence for health technologies (pharmaceuticals or others) all along the technology lifecycle; it consists of two strands: (A) Early dialogues (initial evidence generation) and (B) Post-launch Evidence Generation and Registries.

Scientific advice/early dialogues with HTA bodies and regulatory agencies offer manufacturers an optimal approach for early development of integrated, cross-functional evidence generation plans which, for four key reasons, are particularly applicable to more novel fields like RWE.

1. Early cross-functional alignment on requirements can avoid last-minute shifts in evidence planning that can be very costly; a side benefit of needing to write a briefing book.
2. Participating in scientific advice generates alignment and marks a willingness to communicate with regulators and HTA bodies, meaning that evidence plans are less likely to be dismissed than those without official consultation.[4,23]

Figure 2. Overview of ISA as a Solution to Current Market Changes



3. Advice will be situational and applicable to the exact asset in question, hence avoiding ambiguity in evidence planning due to interpretation of general guidelines without dialogue.
4. It allows manufacturers to enter the conversation on the place of RWE in evidence generation plans outside of political discussions, further helping to shape the current landscape.

The global PRMA landscape is seemingly shifting towards demands for iterative demonstration of value in real-world populations in order for therapies to earn and maintain their place in clinical pathways. In such an environment, ISA represents an opportunity to gain early external and internal cross-functional alignment on RWE strategy and goals for new therapies at launch and beyond (See Figure 2). ■

For more information, please contact Andrea.Schmetz@evidera.com, Stephanie.Wise@evidera.com, Matthew.Bending@evidera.com, or Patricia.Hurley@ppdi.com.

REFERENCES

1. Berger ML, Sox H, Willke RJ, Brixner DL, Eichler HG, Goettsch W, Madigan D, Makady A, Schneeweiss S, Tarricone R, Wang SV, Watkins J, Mullins CD. Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making. *Value Health*. 2017 Sep;20(8):1003-1008. doi: 10.1016/j.jval.2017.08.3019. Epub 2017 Sep 15.
2. Miksad RA, Abernethy AP. Harnessing the Power of Real-World Evidence (RWE): A Checklist to Ensure Regulatory-Grade Data Quality. *Clin Pharmacol Ther*. 2018 Feb;103(2):202-205. doi: 10.1002/cpt.946. Epub 2017 Dec 6.
3. Garrison LP Jr, Neumann PJ, Erickson P, Marshall D, Mullins CD. Using Real-World Data for Coverage and Payment Decisions: The ISPOR Real-World Data Task Force Report. *Value Health*. 2007 Sep-Oct;10(5):326-35.
4. Gannedahl M, Udechuku A, Bending MW. Initiatives Driving Accelerated Access to Medicines in Europe: Review of Recent Concepts and Developments. *Medicine Access @ Point of Care*. 2018 March. doi: 10.1177/2399202618761854.
5. Ng T, Chawla T, Bending MW. PCN293 - What is the Value of Real World Evidence in Oncology in HTA Appraisals in England, France, Canada and Australia? *Value Health*. 2018 Oct; 21(suppl 3):S64. doi: https://doi.org/10.1016/j.jval.2018.09.375.
6. Makady A, van Veelen A, Jonsson P, Moseley O, D'Andon A, de Boer A, Hillege H, Klungel O, Goettsch W. Using Real-World Data in Health Technology Assessment (HTA) Practice: A Comparative Study of Five HTA Agencies. *Pharmacoeconomics*. 2018 Mar;36(3):359-368. doi: 10.1007/s40273-017-0596-z.
7. LSE Research Online. Gill J, Kanavos P, Avouac B, Duncombe R, Hutton J, Jahnz-Rozyk K, Schramm W, Spandonaro F, Thomas M. The Use of Real World Evidence in the European Context: An Analysis of Key Expert Opinion. London School of Economics, London, UK. Available at: http://eprints.lse.ac.uk/68442/. Accessed September 4, 2019.
8. Makady A, Ham RT, de Boer A, Hillege H, Klungel O, Goettsch W; GetReal Workpackage. Policies for Use of Real-World Data in Health Technology Assessment (HTA): A Comparative Study of Six HTA Agencies. *Value Health*. 2017 Apr;20(4):520-532. doi: 10.1016/j.jval.2016.12.003. Epub 2017 Jan 27.
9. Universitat Hamburg Online. Ertl K. Sozialrechtliches Methodenbewertungsrecht – Offen fur "Big Data" und Real World Evidence? 2018. Available at: https://www.jura.uni-hamburg.de/media/ueber-die-fakultaet/personen/ertl-kilian/2018-01-26-vortrag-kilian-ertl.pdf. Accessed September 4, 2019.
10. Deloitte. Analysis 2019 Global Health Care Outlook – Shaping the Future. Available at: https://www2.deloitte.com/global/en/pages/life-sciences-and-healthcare/articles/global-health-care-sector-outlook.html. Accessed September 4, 2019.
11. Goldman DP, Van Nuys K, Cheng WH, Hlavka JP, Pani L, Chassang S, Snowberg E. A New Model for Pricing Drugs of Uncertain Efficacy. *NEJM Catalyst*. December 13, 2018. Available at: https://catalyst.nejm.org/three-part-pricing-drug-model/. Accessed August 29, 2019.
12. eunethta | European Network for Health Technology Assessment. JA3 Work Package 5 - Lifecycle Approach to Improve Evidence Generation. Available at: https://www.eunethta.eu/ja3-archive/work-package-5-life-cycle-approach-to-improve-evidence-generation/. Accessed August 29, 2019.
13. Evidera. Insights from the HTAi 2019 Annual Meeting. Available at: https://www.evidera.com/wp-content/uploads/2019/09/2019_HTAi-Annual-Meeting-ebook_FINAL.pdf. Accessed September 6, 2019.
14. Shah NN, Maatman T, Hari P, Johnson B. Multi Targeted CAR-T Cell Therapies for B-Cell Malignancies. *Front Oncol*. 2019 Mar 12;9:146. doi: 10.3389/fonc.2019.00146. eCollection 2019.
15. NHS Clinical Commissioners. Items Which Should Not Routinely be Prescribed in Primary Care: Guidance for CCGs. Version 2, June 2019. Available at: https://www.england.nhs.uk/wp-content/uploads/2019/08/items-which-should-not-routinely-be-prescribed-in-primary-care-v2.1.pdf. Accessed September 4, 2019.
16. Bundesministerium fur Gesundheit. Gesetz fur Mehr Sicherheit in der Arzneimittelversorgung. Available at: https://offenegesetze.de/veroeffentlichung/bgbl1/2019/30. Accessed September 4, 2019.
17. Bending M. Early Integrated Scientific Advice: A Key to Optimal PRMA? Presented at World Pharma Pricing and Market Access Congress, March 19-20, 2019, in Amsterdam, Netherlands.
18. European Medicines Agency. Moseley J. Regulatory Perspective on Real World Evidence (RWE) in Scientific Advice. 17 April 2018. Available at: https://www.ema.europa.eu/en/documents/presentation/presentation-regulatory-perspective-real-world-evidence-rwe-scientific-advice-emas-pcwp-hcpwp-joint_en.pdf. Accessed September 4, 2019.
19. FDA | U.S. Food & Drug Administration. Real-World Evidence. 2019. Available at: https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence. Accessed August 29, 2019.
20. Osipenko L, Michel S. HTA Scientific Advice - Is it Becoming More Important? *The Evidence Forum*. 2018 Fall. Available at: https://www.evidera.com/wp-content/uploads/2018/10/01-Interview-with-Dr.-Leeza-Osipenko_Fall2018.pdf. Accessed August 29, 2019.
21. Schunemann HJ. All Evidence is Real World Evidence. March 29, 2019. *thebmjopinion*. Available at: https://blogs.bmj.com/bmj/2019/03/29/holger-j-schunemann-all-evidence-is-real-world-evidence/. Accessed August 29, 2019.
22. HTAi. Tunis S, Sampietro-Colom L. Real-World Evidence in the Context of Health Technology Assessment Processes – from Theory to Action. HTAi Policy Forum Series Newsletter. February 2019. Available at: https://htai.org/wp-content/uploads/2019/03/HTAi_Global-Policy-Forum_newsletter_20190222.pdf. Accessed September 4, 2019.
23. European Medicines Agency. Scientific Advice Leads to Stronger Applications from Industry. April 17, 2015. Available at: https://www.ema.europa.eu/en/news/scientific-advice-leads-stronger-applications-industry. Accessed September 4, 2019.

Increase Study Awareness and Patient Engagement with the Use of Branded Study Materials

Brenda Garrison
Senior Director Project Management, Therapeutic Area Lead – Hematology/Oncology, Peri- and Post-Approval Interventional Studies, Evidera

Kristin Kluthe, PMP
Director Project Management, Peri- and Post-Approval Interventional Studies, Evidera

Ethel Pilati, MSc
Associate Director Project Management, Peri- and Post-Approval Interventional Studies, Evidera

Background

In recent years, traditional communication mechanisms regarding clinical studies have changed significantly. Patients no longer take a back seat in healthcare decision making; therefore, strategies to attract and engage them must evolve to meet their expectations. The era of patient centricity is here, and patient perspectives must be taken into account every step of the way through product development and commercialization.

The shift toward patient centricity is partly due to advancements in technology and communication. Additionally, collaboration with patient advocacy groups and a surge in social media platforms provide patients and caregivers with more options to find the best study to meet


Brenda Garrison


Kristin Kluthe


Ethel Pilati

their needs throughout their disease journey. Furthermore, with an ever-increasing number of clinical studies around the world, competition for enrollment continues to be a challenge.

With patients taking a more proactive role in their own healthcare decisions, there is an increasing need to adopt innovative approaches for patient recruitment and retention that highlight the benefits of clinical research and differentiate your clinical study from other choices. Study branding – establishing a unique name and visual identity – can be a highly effective tool to increase study awareness, interest, and immediate brand recognition for site personnel, patients, and caregivers.

Branding Considerations

Once a company has decided there is benefit in branding a clinical study, there are many factors and stakeholders to consider before moving forward.

- What does the current and emerging competitive study landscape look like?
- How many other studies are being conducted in the same space?
- What are the specific objectives for branding the study?
- Is the intention to use the study branding in marketing activities once the product has been launched?
- Who is the target audience or audiences?

A powerful and successful approach to study branding should start at the study design phase and it is important at this point to consider several factors before moving forward.

- **Patient population**. Pay attention to your audience and what speaks to them specifically. Is the study focusing on the pediatric or adult population? Women or men? Predominantly low or high income? Different patient segments will relate to branding in various ways so be sure you are considering your audience. A good resource for input in this area could be patient advocacy groups or other groups that could help identify potential trigger words or images that may have a negative effect on the patient population.
- **Geographic concerns**. Certain words, phrases, and images may have different meanings depending on the location of your target audience, specifically from country to country, but also potentially within countries. For example, a colloquial term or play on words quite familiar in one part of the United States may fall flat in other areas of the country. Do your homework and test branding elements across various geographic regions before finalizing your branding.
- **External considerations**. As with any clinical study communications, branding elements must be regulatory compliant; it is, therefore, important to confirm any branding name or graphics meet necessary guidelines and can stand up to review board scrutiny.

Branding Strategy

As the creative phase begins it is important to remember that any designs and/or messaging needs to connect with patients and their families or caregivers. The selection of an impactful study name or acronym needs to relate to the patient population and the inclusion of appealing visual aspects, such as graphics, photos, illustrations, etc., should be used to help simplify the message and grab the attention of your audience.

Many study and drug descriptions use scientific jargon that can make it challenging for patients to understand. Developing recruitment materials with a patient audience in mind, speaking in patient-friendly terminology, and clearly illustrating the benefits to the patient are more likely to attract participants and may have a significant impact on enrollment timelines.

> ... it is important to remember that any designs and/or messaging need to connect with patients and their families or caregivers. The selection of an impactful study name or acronym needs to relate to the patient population ...

Branded materials must be high quality, professional, and appeal to the targeted audience. Attention should be paid to design factors such as color, fonts, images, tone, consistency, and how each branded piece will be used. It is important to use a designer who is experienced in these elements and can produce a full spectrum package of content. A professional designer can also ensure that research previously done on patient populations, geographic concerns, and external considerations is considered during the development of these materials. Patients and caregivers need to have confidence that the study they are entering is safe and beneficial, and high quality, professional materials are an important aspect of building that image. In the internet era patients can easily access information about drug competitors, drug safety, and efficacy profiles; therefore, any communications or information shared on the study should inspire the confidence patients require to comfortably select your study if it best fits their needs.

Conclusion

Study branding is a critical aspect of study planning and can have significant impact on the success of a study. Early discussions about the benefit of study branding, along with key input from patient advocacy groups and alignment with regulatory authorities and ethics committees, will raise awareness and reinforce the study through the consistent use of graphics, images, and visuals via numerous forms of communication. While this article focuses on key considerations in a decision to brand and how to best connect with patients for recruitment and retention purposes, there are a myriad of other considerations and benefits that could arise from branding your study (See Figure 1). As study options increase in certain therapeutic areas and companies look to decrease timelines and increase brand recognition, expect study branding to grow as companies seek a competitive advantage to achieve product success. Not all studies need to be branded, but it is highly recommended that you consider the option when designing your clinical study. ■

Special thanks to Christina Kirkpatrick, Senior Account Director, Business Development, PPD who contributed to this article.

For more information, please contact Brenda.Garrison@ppdi.com, Kristin.Kluthe@ppdi.com, or Ethel.Pilati@ppdi.com.

Figure 1. Considerations and Benefits of Study Branding

Virtual Trials and Real-World Evidence Data Collection

Identifying Core Needs and Defining "Virtual Trials"

Mariah Baltezegar, MBA
Executive Director, Head of PPA Virtual Trials, Real-World Evidence
Evidera

Debra Schaumberg, SCD, OD, MPH
Vice President, Scientific Affairs, Real-World Evidence, Evidera

There is increasing recognition of the need for more fit-for-purpose evidence in development of therapeutics (drug, device, and digital). In the US, in response to the 21st Century Cures Act, the US Food and Drug Administration (FDA) has developed a framework for evaluating real-world evidence (RWE) to support approvals of new indications for previously approved therapeutics and address post-approval study requirements. The collection of RWE is enabled by virtual trials, or decentralized approaches to patient identification and data collection. To inform this approach, we must first understand who the stakeholders are and what their needs are as well as begin speaking the same language around virtual trials; there is no widespread consensus on terminology. Understanding these foundational needs and aligning on definition enables early planning to incorporate such strategies.

Mariah Baltezegar

Debra Schaumberg

Understanding the Needs

Reaching More Patients

Strict inclusion/exclusion criteria and research center-based infrastructure do not serve patients who live remotely, lack transportation, or lead busy lives. This separation of infrastructure makes reaching a heterogenous population challenging. Generally, clinical care facilities do not conduct research and research facilities are either commercial research centers or large, academic teaching centers. Patients who use providers that exist outside of those facilities generally receive existing medical care rather than participate in research. To ensure we are capturing data from a representative sample of patients, we must find ways to *reach a wider group of patients*. It stands to reason, if patients in the research cohort are more homogeneous than the patient population that would be likely to receive the approved therapy, their data may not be generalizable to the greater population. An inherent tradeoff arises between randomized control design choices aimed at enhancing internal validity with those more pragmatic choices that would aid generalizability. For example, registration trials increasingly tend to enroll relatively small samples of highly selected patients at sites with experienced investigators under ideal conditions, collecting large amounts of very specific data that are often not a routine part of clinical care.

Almost 15% to 20% of trials do not enroll a single patient.[1] To continue to evolve the development of fit-for-purpose evidence to inform the real-world use of approved therapeutics, we must *make research more accessible*. Depending on the research question, a patient may be happy to complete a patient-reported outcome (PRO) or telemedicine visit in their home or at work but not willing to go to a brick and mortar site location to perform the same activities. In this way, we must weigh the burden of participation versus the value of the information. In the United States, 70% of potential patients live over two hours away from the nearest traditional study site,[2] which limits participation and leads to higher potential for subject dropout as patients can incur costs and lost time from work associated with traveling to the study site. As virtual trials aim to reduce or eliminate site visits by bringing the trial closer to a patient's home, more patients have the potential to participate.

Decreasing Burden

Over time, traditional randomized trial protocols have become increasingly more complex. To increase participation and retention, we must *decrease the burden of participation for patients and their caregivers*. Many clinical trials still rely on 1990s-era processes, and many R&D functions have yet to fully leverage real-world evidence (RWE), genomics information, and emerging data sources such as the Internet of Things (IoT), wearables, mobile apps, and more.[2] The use of digital technologies such as eRecruitment, eConsent, ePROs, wearables, and collection of data directly through patients' electronic medical records, which many virtual trials also employ, allow patients to integrate a trial more or less seamlessly into their lives, therefore reducing burden and decreasing dropout rate. The average dropout rate from trial protocols is 30% based on research by both the Tufts Center for the Study of Drug Development and Forte Research[3] and approximately 40% of patients do not end up adhering to trial protocols. This can impact the outcome of a trial and may introduce bias in the assessment of efficacy and safety. These technologies can also help with protocol compliance, as many have the capacity to proactively remind patients to follow a study's protocol.

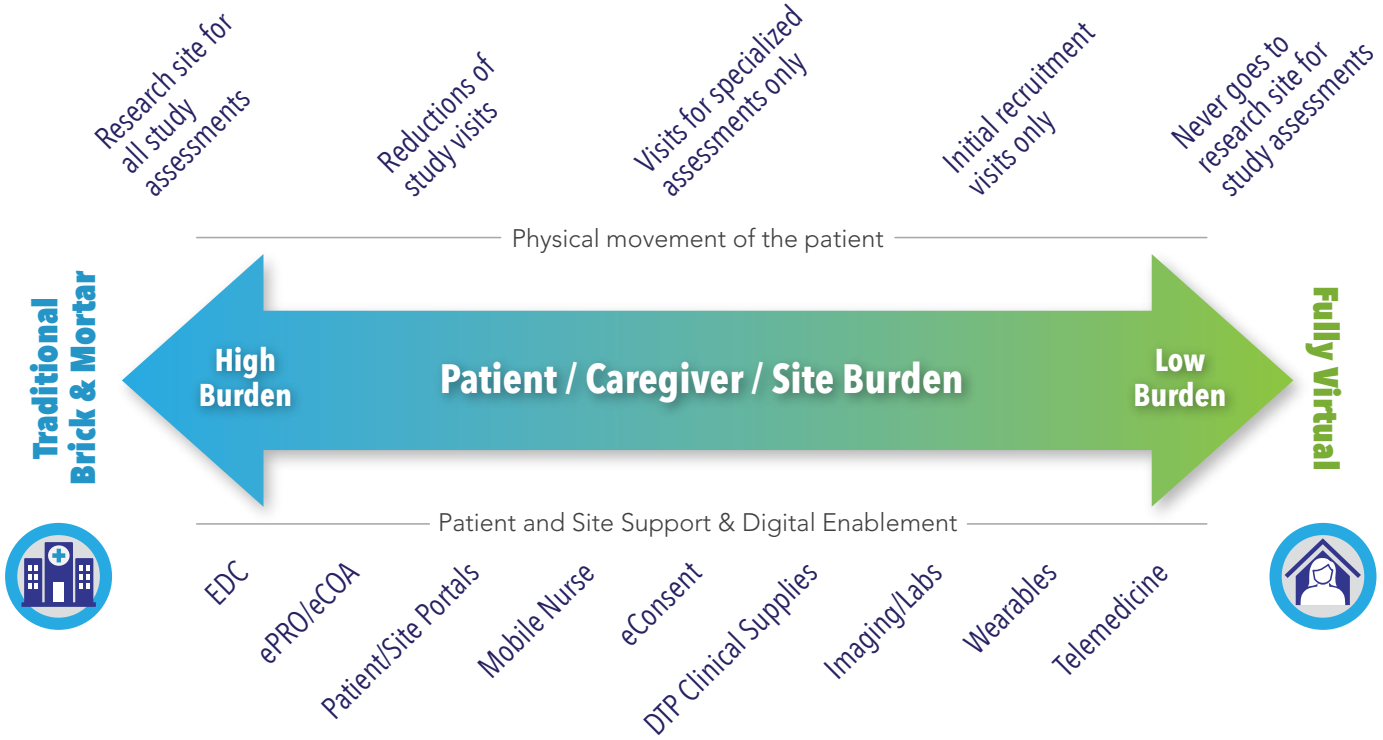
> As virtual study models center around placing patients at the center of a trial and allowing them to participate more easily, they can easily be applied to ***enable pragmatic trials*** to collect rich, real-world data.

Reducing the cost of therapy development is also another key need, though it is early in the lifecycle of virtualization to say where cost savings may be realized. Virtualizing trials can theoretically save time and resources by reducing the number of investigators and sites. The fewer sites a trial utilizes, the lower costs tend to be. Investigator fees are responsible for 40% to 60% of a trial's budget,[4] paying sites for patient visits costs between $3,000 and $7,000 per visit,[5] and site activation and management can make up an additional 25% to 30%.[4] What we do know is that a virtual approach enables the conduct of large-scale studies that are otherwise cost prohibitive, allowing for fewer sites or even no sites depending on the research question being asked and the types of assessments needed. As virtualization continues to gain momentum and mature, we anticipate more proof points will emerge regarding areas of cost savings.

Putting the Patient at the Center

A renewed focus on patients and their involvement in healthcare, treatment decisions, and increasingly in designing research is also driving discussions of the role of RWE and pragmatic trials. As virtual study models center around placing patients at the center of a trial and allowing them to participate more easily, they can easily be applied to *enable pragmatic trials* to collect rich, real-world data. Pragmatic trials draw on the substantial methodological, bias-reducing advantages of random allocation of health interventions combined with the real-world setting of an observational study and naturally lend themselves to virtual approaches. A burgeoning selection of patient/physiological monitoring devices with the potential to provide real-time data on important indicators is an emerging area of innovation with likely applications in the

Figure 1. Considerations When Assessing Virtualization



EDC = electronic data collection; ePRO/eCOA = electronic patient-reported outcomes/electronic clinical outcome assessments; DTP = direct to patient

pragmatic trial setting. For certain indications, physiological monitoring may be highly predictive of a clinically relevant endpoint, and real-time collection of symptom scores is another potential application. Regulatory guidance on the use of mobile apps for reporting adverse drug reactions (ADRs) and use of social media is under development.[6] To fully realize the value that can be added through more widespread conduct of pragmatic trials, the field must realize a paradigm shift to incorporate data and operational platforms that can capitalize on data capture through electronic health records (EHRs), registries, patient-reported outcomes (PROs), etc., and enrollment infrastructures within integrated health systems. Already gaining traction in the peri- and post-approval time period, moving forward, more pragmatic elements will begin to be introduced earlier, during the formulation of the clinical development plan.

The Many Names of "Virtual" Trials

Although there are examples of virtual trials that date back several decades,[7,8] the incorporation of virtual trials into commercial therapeutic development and product lifecycle management is an emerging concept and there is no uniform agreement on definitions. Although non-interventional studies are not typically considered a "trial," the term has been applied in the context of both interventional as well as non-interventional studies.

The most common terms used to define this paradigm in which studies are conducted either partially or entirely remotely include:

- **Virtual trials.** An umbrella term used to describe collecting data from patients in their local healthcare environment versus requiring them to go to a clinical research site or other brick and mortar location. This can be accomplished with or without technology and moves research away from the traditional site visit model to a more disseminated model where patients can participate from their homes and nearby surroundings. Virtual trials have been conducted for decades and now, with the advent of enabling technologies, are often digitally enabled.
- **Digitally enabled trials.** These are studies that use digital technologies to enhance the efficiency of a trial, including well-established technologies such as electronic clinical outcome assessments (eCOAs) or electronic PROs (ePROs) to newer technologies such as telemedicine and wearables. Studies have been

incorporating certain digitally enabled technologies for decades. The key now is to integrate multiple technology solutions for a trial either with a single vendor or, at minimum, with a solid solution for integration of data from multiple technology partners.

- **Decentralized trials.** This is a term describing the movement away from the site-based trial model, in which all trial activities are centered on the site, to more of a model where patients are the primary focus. This term is used by regulatory agencies including the FDA and the Medicines and Healthcare products Regulatory Agency (MHRA) and it has been reported that the FDA has created a working group on the topic of decentralized trials that will be charged with outlining standards for this new space.[8]

There are three dimensions to consider when assessing virtualization, including burden on the patient, caregiver, or site; physical movement of the patient; and, support and digital enablement (See Figure 1).

Not only does the pharmaceutical industry recognize the need to transform RWE collection, but regulators do as well. In January 2019, the commissioner of the FDA at that time, Scott Gottlieb, MD, shared his goals including supporting seamless integration of digital technologies in clinical trials and bringing clinical trials directly to the patient. Virtual trials enable efficient collection of RWE by bringing the trial to the patient instead of the patient to the trial. Whether we are referring to truly virtual trials, decentralized trials, or digitally enabled trials, each has its merits to facilitate right-sized RWE collection to support the development and commercialization of therapeutics. ■

For more information, please contact Mariah.Baltezegar@evidera.com or Debra.Schaumberg@evidera.com.

REFERENCES

1. The Numbers Game: Boosting Clinical Trial Enrollment. *Pharmaceutical Technology*, February 5, 2014, Available at: http://www.pharmaceutical-technology.com/features/featurethe-numbers-game-boosting-clinical-trial-enrolment-4171654/. Accessed September 1, 2019.
2. Deloitte's Life Sciences & Health Care Blog. A View from the Center. Available at: https://blogs.deloitte.com/centerforhealthsolutions/digital-rd-four-ways-to-maximize-patient-engagement-in-clinical-trials/. Accessed September 1, 2019.
3. Forte. Lopienski K. Retention in Clinical Trials – Keeping Patients on Protocols. June 2015. Available at: https://forteresearch.com/news/infographic/infographic-retention-in-clinical-trials-keeping-patients-on-protocols/. Accessed September 1, 2019.
4. Araujo DS. Measuring the Financial Impact of Remote (Digital) Clinical Trials. Clinical Leader. Guest Column, January 20, 2019. Available at: https://www.clinicalleader.com/doc/measuring-the-financial-impact-of-remote-digital-clinical-trials-0001. Accessed September 1, 2019.
5. Fast Company. The Search for New Drugs is Coming to Your House. Available at: https://www.fastcompany.com/90229910/virtual-clinical-trials-are-bringing-drug-development-home. Accessed September 1, 2019.
6. Schaumberg DA, Mihos M, Payne K, Chen D. The Drive Towards Pragmatism in Randomized Trials: Are We There Yet? *The Evidence Forum*. November 2017. Available at: https://www.evidera.com/wp-content/uploads/2017/10/The-Evidence-Forum-2017-November.pdf. Accessed September 2, 2019.
7. Buring JE, Hennekens CH. Cost and Efficiency in Clinical Trials: The U.S. Physicians' Health Study. *Stat Med*. 1990 Jan-Feb;9(1-2):29-33.
8. US Food and Drug Administration. Breaking Down Barriers Between Clinical Trials and Clinical Care: Incorporating Real World Evidence into Regulatory Decision Making. January 28, 2019. Available at: https://www.fda.gov/news-events/speeches-fda-officials/breaking-down-barriers-between-clinical-trials-and-clinical-care-incorporating-real-world-evidence. Accessed September 2, 2019.

Pragmatic Randomized Trials
Considerations for Design and Implementation

Andrew Bevan MRes, MRSB, CBiol
Senior Director Project Management, Peri- and Post-Approval Studies, Evidera

Paul Biedenbach, BA
Executive Director Operations, Medical Communications, PPD

Ariel Berger, MPH
Executive Director, Integrated Solutions, Real-World Evidence Evidera

Introduction

The 21st Century Cures Act (Cures Act),[1] which became law in the United States December 13, 2016, has highlighted the need for robust real-world data to demonstrate effectiveness and safety of healthcare innovations that meet the requirements of regulators and payers alike. Included in the Act is an agreement to fund and accelerate cancer research and overall medical product development and delivery, as well as increase choice in, access to, and quality of American healthcare. One result of the Act has been to increase interest from both industry and regulatory authorities, such as the US Food and Drug Administration (FDA), in pragmatic randomized trials (PRTs). In December 2018, the FDA's Framework for Real-World Evidence Program[2] was published, which *"created a framework for evaluating the potential use of real-world evidence (RWE) to help support the approval of a new indication for a drug already approved under section 505(c) of the FD&C Act or to help support or satisfy drug post-approval study requirements."*

The industry has yet to feel the impact of this paradigm shift, not least because the traditional explanatory randomized controlled trial (RCT) utilizing surrogate


Andrew Bevan


Paul Biedenbach


Ariel Berger

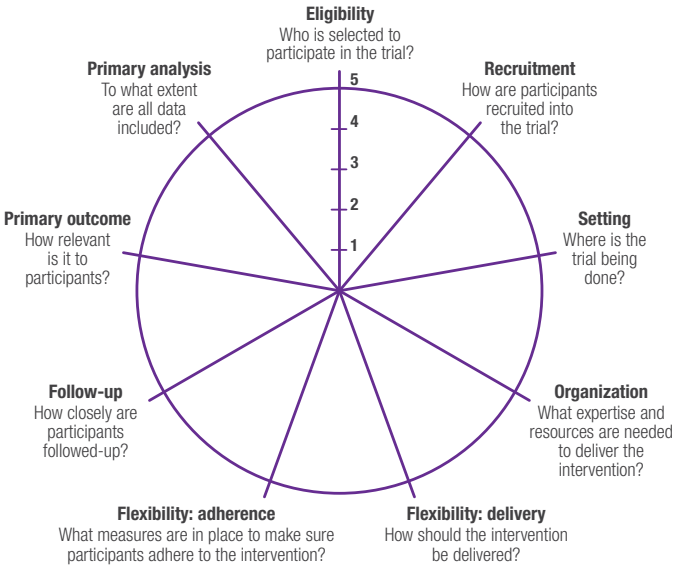
endpoints to establish efficacy and safety in a highly selected population under optimal conditions has been the gold standard for researchers and regulators alike for many decades. These trials, which generate high-quality robust data with high intrinsic validity upon which to base conclusions about causal relationships, answer the explanatory question "is the intervention efficacious and safe in tightly controlled, artificial conditions?" However, they ignore the more pragmatic question "is this an effective and safe option for my patient?" The pragmatic trial design was developed to answer the latter, which is a key question that can inform potentially life-altering decisions required by payers, clinicians, and even patients themselves.

Unlike randomized trials, pragmatic studies use "typical" clinical settings to examine real-world outcomes such as survival, utilization of healthcare services and/or pharmacotherapy, and overall cost of care. Most of these outcomes can be obtained from electronic health records (EHRs), which can shorten study timelines and reduce budget while still providing high-quality information. Pragmatic studies aim to generate evidence and conclusions based on real-world practice that are highly relevant to payers, healthcare providers (HCPs), and ultimately policy makers as they look to gather information to make treatment-related decisions. However, these studies have suffered from concerns of relatively low internal validity due to issues of outcome misclassification and other forms of bias (e.g., selection bias, confounding by indication). These issues can increase the risk of spurious associations between treatment(s) and associated outcomes related to effectiveness and/or safety, thereby reducing the reliability of the conclusions that can be drawn regarding cause and effect, and subsequently limiting their value to regulators. Given the "low intensity" of investigator oversight during the conduct of pragmatic studies, there also are concerns around the quality of information collected – particularly, key outcome measures.

Pragmatic Randomized Trials

PRTs represent a hybrid between traditional randomized controlled clinical trials that have been the gold standard for regulatory decision making, and pragmatic, observational research studies that are often used to generate real-world evidence to support health technology assessment (HTA) and payer decision making. A well-designed PRT that maximizes external validity, but also controls for confounding (including but not limited to selection bias) in order to maintain high levels of internal validity, could theoretically be used to generate evidence that would meet both regulatory and payer requirements. A number of tools have been developed to help researchers design pragmatic trials.[3-5] One such validated tool is the PRagmatic Explanatory Continuum Indicator Summary Version 2 (PRECIS-2),[5] which is a 9-spoked wheel, with each spoke representing a domain that denotes a key element of trial design (Figure 1). Each domain is scored on a 5-point Likert scale ranging from explanatory to pragmatic (i.e., 1=very

Figure 1. The PRagmatic-Explanatory Continuum Indicator Summary 2 (PRECIS-2) Wheel (*Adapted from Louden, et al.*[5])

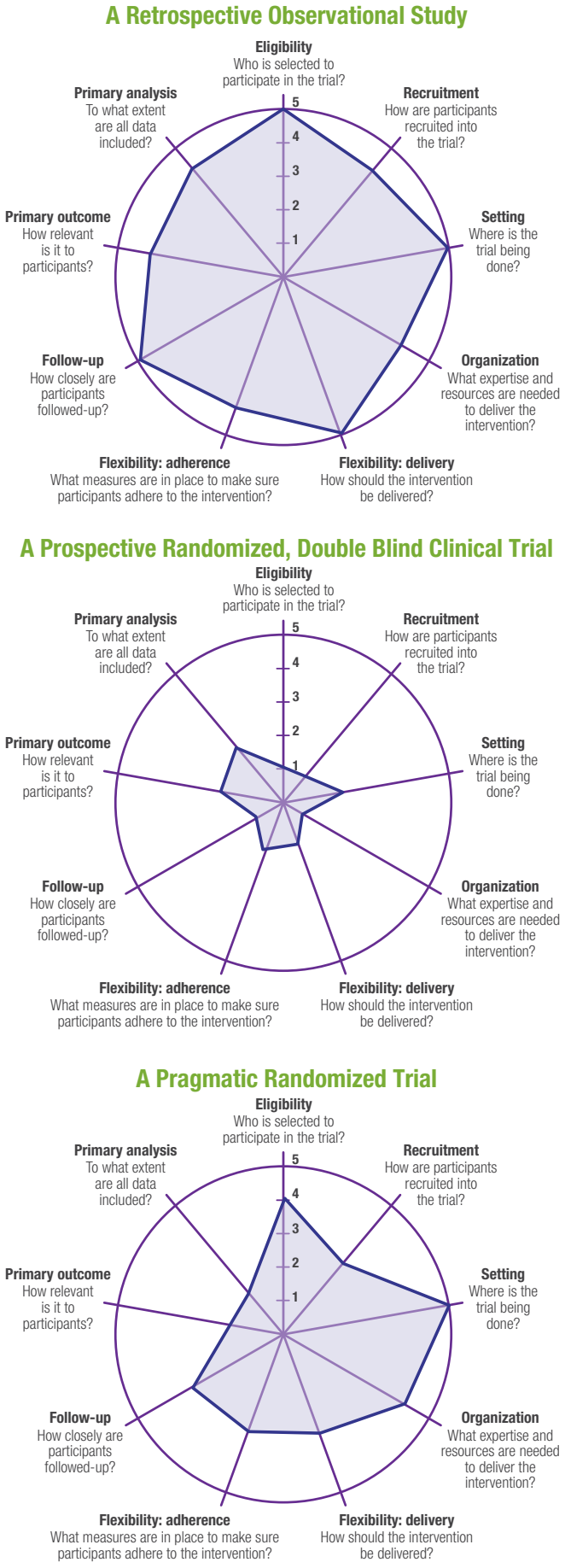


explanatory, 2=rather explanatory, 3=equally pragmatic/explanatory, 4=rather pragmatic, 5=very pragmatic). Trials that are predominantly explanatory in their design generate spoke and wheel diagrams that are close to the hub, whereas those with a more pragmatic approach produce diagrams that are closer to the rim. In reality, few trials are purely explanatory or purely pragmatic, and for the most part, a well-designed PRT that maintains high levels of external *and* internal validity will seek to strike an optimal balance between the two study types, thereby producing a diagram that would be somewhere in the middle of the wheel (and potentially an "uneven" wheel, with aspects more pragmatic pulling the circle closer to the rim and those more explanatory drawing the corresponding point closer to the hub). Representative diagrams for these designs are shown in Figure 2. Design choices should be based primarily on the research question(s) being posed; for example, in a pragmatic cardiovascular outcomes trial, more importance may be placed on high scores on the Eligibility, Primary Outcome, Setting, and Follow-up domains, whereas a trial investigating an intervention in a post-surgical intensive care setting may alternatively preferentially weight the Recruitment, Flexibility-delivery, and Primary Analysis domains.

Real-World Outcomes and Endpoints

One of the challenges of designing effective PRTs is the choice of outcomes and endpoints. The term outcome is used here to mean a measured variable or event of interest (e.g., time to first occurrence of a composite outcome such as myocardial infarction [MI], stroke, or cardiovascular death, which collectively are referred to as major adverse cardiovascular events [MACE]), whereas an endpoint refers to an analyzed parameter that is expected to change over

Figure 2. Hypothetical PRECIS-2 Spoke and Wheel Diagrams



time as a result of an intervention (e.g., change in LDL-C from baseline). For a PRT to meet the requirements of both regulators and payers, it is important that the selected endpoints and outcome measures resonate with key stakeholders (patients, payers, regulators, and healthcare providers), and be defined with sufficient sensitivity (typically more important for safety) and specificity (typically more important for effectiveness estimates) to translate the trial objectives into precise definitions of treatment effect. In addition, endpoints and outcome measures that are routinely available from EHR will render the study more pragmatic as it reduces the need to interact with those running the study (each such interaction moves the patient further from typical care and more towards protocol-mandated care).

In the routine clinical setting, intercurrent events can occur following an intervention – including treatment discontinuation or switching, or use of alternative or contraindicated medications – that can result in treatment effects being misinterpreted. Selecting endpoints and outcome measures without first considering the impact of these intercurrent events will result in uncertainty over the treatment effect, and potentially place a study at risk of not meeting its objectives. The impact of intercurrent events can be controlled for by randomization; however, it may not always be practical or even possible to randomize on an individual subject level, but instead other methods may need to be employed (e.g., cluster randomization [randomizing at the site level] or crossover designs) which can add to complexity of the trial design and analysis. Bias can also be introduced into PRTs through lack of ability to mask treatments. This can be addressed to a certain extent by selecting clinically objective outcomes (e.g., stroke, hospitalization due to non-fatal MI, tumor size), but this may not always be possible (e.g., in studies of Alzheimer's disease, where clinical outcome assessments [COAs] are subject to human interpretation); moreover, structural changes (e.g., items measured using surrogate imaging endpoints) may not translate into clinically meaningful change. Ultimately the selection of a primary endpoint or outcome will be driven by the research question(s) and how to best define the effect(s) of the treatment under study while controlling through design choices for the presence of varied intercurrent events. This topic is addressed in ICH-E9-R1, which introduces the estimand framework to link the trial objectives, the study population, and the variable (or endpoint) of interest to intercurrent events reflected in the research question to more effectively translate the trial objective(s) into a precise definition of the treatment effect(s) under investigation.[6] This revision to ICH guidance will undoubtably shape the approach to the design of randomized clinical trials, especially PRTs, in the future.

The Rise of Health Informatics and Big Data

The increasing availability of rich EHR potentially linkable to medical claims data, and our ability to mine those data using artificial intelligence (AI) and other advanced analytic

methods has expanded the possibilities for implementing embedded PRTs that reduce operational complexity, timelines, and cost, while still allowing for valid comparisons between treatments. AI has enabled computable phenotypes with the precise clinical characteristics that comprise the relevant study population, and clinical and economic outcomes of interest, *all from the same data source(s)*. One example of a real-world data source that has been widely used in the post-marketing evaluation of medicines is the Swedish Healthcare Quality Registries, which collect nationwide clinical data, encompassing a specific disease, intervention, or patient group that is highly relevant to regulators and HTAs.[7] One particular advantage of the Swedish Quality Registries is the ability to link data on specific patient phenotypes with treatments and outcomes. The VALIDATE-SWEDEHEART Trial is an example of a PRT that utilized a Swedish registry platform to compare bivalirudin versus heparin in ST-segment myocardial infarction (STEMI) and non-ST segment myocardial infarction (non-STEMI) patients undergoing percutaneous coronary intervention (PCI) on the composite endpoint of MI, all-cause mortality, and major bleeding.[8] It is included here as a case study to demonstrate the potential of big data within which PRTs can be conducted.

The use of coding algorithms to extract clinical outcomes from EHRs has been gaining traction in pharmacological studies over the past decade. For example, and specific to cardiovascular research, International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes for acute MI have been shown to have a positive predictive value (PPV) of ≥95% compared to manual chart review.[9,10] However, it may not always be clear which code on a particular record to use (each record can have multiple codes), or whether a particular diagnosis relates to the principal discharge diagnosis (i.e., the diagnosis that best describes the reason for the admission), and therefore algorithms that rely on ICD-9-CM diagnoses alone may not translate to a broad clinical research setting. This raises the need for more advanced techniques to identify MACE that may include medication and laboratory data. One such approach used diagnosis codes, procedure codes (in Current Physician's Terminology, 4th Edition [CPT-4] format), and laboratory test results, resulting in a more accurate algorithm to identify MACE (i.e., PPVs between 90% to 97% compared to manual review)[11] that could be readily adapted for use in other pragmatic cardiovascular trials (assuming access to comparable data types).

EHR and claims data have been used to generate RWE in a number of therapeutic areas including but not limited to cardiovascular studies and oncology. One example of the former is a real-world counterpart to the COMPASS pivotal, randomized, multicenter, randomized clinical trial, in which patients with existing and stable coronary artery disease (CAD) or peripheral artery disease (PAD) were randomized to receive low-dose rivaroxaban plus aspirin versus aspirin only[12]; findings from COMPASS, which was stopped early

Pragmatic RCT Case Study

VALIDATE-SWEDEHEART-Trial (Bivalirudin versus Heparin in ST-Segment and Non-ST-Segment Elevation Myocardial Infarction in Patients on Modern Antiplatelet Therapy in the Swedish Web System for Enhancement and Development of Evidence-based Care in Heart Disease Evaluated According to Recommended Therapies Registry Trial)

- **Multicenter, prospective, randomized, open-label design**
- **Utilized a national registry platform to identify eligible patients and extract clinical outcomes using ICD9 and ICD10 diagnosis codes**
- **The registry includes patients admitted to the hospital because of symptoms suggestive of acute coronary syndrome (ACS), and patients undergoing coronary angiography/ angioplasty or heart surgery**
- **The study consented and enrolled 6,006 patients (3,005 STEMI, 3,001 NSTEMI) undergoing PCI and treated with P_2Y_{12} inhibitors at 22 centers**
- **Patients randomized 1:1 to receive bivalirudin or heparin**
- **Primary outcome was composite endpoint of MI, all-cause mortality, and major bleeding at 6 months**
- **The study concluded that the rate of composite of death from any cause (MI or major bleeding) was not lower among patients who received bivalirudin compared to heparin**

due to "overwhelming efficacy," provided the evidence needed to expand existing indications for rivaroxaban to include secondary prevention of MACE and major adverse limb events (MALE).[13] In the real-world study, which was run in parallel to COMPASS to demonstrate the burden of MACE and MALE in clinical practice prior to this expanded indication, key trial outcomes (including MACE, MALE, and the incidence of major bleeds), were estimated based on relevant diagnosis codes associated with claims submitted by providers in relevant settings of care (e.g., MI required a relevant principal diagnosis resulting from a visit to an emergency room or admission to hospital).

While access to RWE through EHR and claims data is fairly robust in key markets, the same cannot be said for emerging markets where access has been limited. With greater attention on the Asia Pacific market, demand for access to RWD is growing and, luckily, so is access. For example, PPD and Happy Life Tech (HLT), a Chinese medical AI company with an established relationship with and access to EHR from more than 100 leading hospitals across over 20 provinces in China, entered into an exclusive and unique collaboration.[14] With data representing the health experience of over 300 million patients, HLT data will allow more RWE studies to be done using Chinese patient data, and this should open up the potential to perform embedded global PRTs in this important emerging market. Using statistical methods of meta analyses, information from HLT could be aggregated with comparable data from other countries of interest, thereby potentially extending the power of this "hybrid" study design globally.

Challenges of Interoperability

In addition to ensuring algorithmic approaches to real-world data are generalizable across different sources (e.g., across EHR types, healthcare claims from various insurance payers) and different pragmatic research settings, the ability for one software system and associated data formats to interact with others (i.e., interoperability) represents a challenge to conducting multicenter/multi-country PRTs. Until recently, the mainstay for tackling this obstacle has been to implement common data models (CDMs) such as the FDA's Sentinel Initiative[15,16] to standardize data across multiple sources for research purposes. However, even though sites may format data according to a pre-defined CDM, CDMs require data to be mapped which can result in loss of detail, as information not common to all participating sites/systems tends to be omitted from the final CDM-driven data set. Another answer could be HL7's Fast Healthcare Interoperability Resources or FHIR[17] (pronounced "fire"). FHIR is a draft data standard and Application Programming Interface (API), which is quickly becoming the industry standard for exchanging healthcare data between disparate software systems, including wearable devices,[18] and has great potential to be an application-based solution to the challenges of interoperability. FHIR aims to provide developers with a user-friendly solution to build applications that enable healthcare data to be accessed irrespective of the EHR system being used and is the data standard that has been adopted by federal agencies and healthcare providers in the US, including the Department of Health and Human Services (HHS), the Veterans Administration, and the Department of Defense; the National Health Service (NHS) in the UK also has adopted FHIR. Recently the Centers for Medicare and Medicaid Services (CMS) announced the launch of a pilot program that leverages FHIR to enable clinicians to directly access Medicare claims data, which according to CMS will "*fill in information gaps for clinicians, giving them a more structured and complete patient history with information like previous diagnoses, past procedures, and medication lists.*"[19] Evidera is already using FHIR to build bespoke data integration solutions to support both retrospective and prospective (including pragmatic) research for our clients that incorporate data from multiple diverse EHR data sources into a single cloud-based platform to support real-world evidence generation and address the challenges of interoperability.

Challenges of Missing Data

Further challenges encountered when performing PRTs are variation in intervals to disease status/check-in and the ability to capture outcomes over time to avoid missing events and incomplete data. The importance of this as a trial design consideration is obviously dependent on

Figure 3. Supporting Remote Patient-Reported Outcomes Data Collection via Global Contact Centers

the nature of the condition and the treatment effect(s) of interest (e.g., in oncology, the timing of assessments may be very heterogenous in the real-world setting and this must be taken into account in the trial design). EHR data are a rich source that captures encounters that occur within specific care settings. However, due to the fragmented nature of the US healthcare system, encounters that occur outside of participating settings are not likely to appear in EHR or may be incomplete. One way to address this "missingness" potential is to supplement EHR sources with information from other sources, including but not limited to claims data, patient-reported outcomes, and direct-to-patient follow-up. This approach is being taken with the ground-breaking ADAPTABLE trial (Aspirin Dosing: A Patient-centric Trial Assessing Benefits and Long-Term Effectiveness) to compare the effectiveness of two different widely used doses of aspirin to prevent MI and stroke in patients with heart disease.[20] This trial, which is being conducted in the US, is a collaboration between the National Patient Centered Research Network (PCORnet) and Duke Clinical Research Institute (DCRI) and has recently completed enrollment of the planned 15,000 patients. The trial utilizes a combination of routine querying of EHR via the PCORnet CDM; surveillance data and medical claims data from CMS; and patient-reported outcomes confirmed through contact with DCRI personnel via a centralized call center, to capture endpoints for hospitalizations for MI, stroke, and death events.

This ability to maintain direct-to-patient contact in a long-term, follow-up study is important to ensure that outcomes are not missed and that patients are retained in follow-up. To facilitate comprehensive capture of relevant outcomes, access to global contact center capabilities to support pragmatic clinical trials is important (See Figure 3). These types of call centers should have a comprehensive understanding of the regulatory, cultural, and logistical complexities associated with providing clinical trial support services across the globe, ideally with 24/7/365 coverage to address patient inquiries and needs during study conduct.

Conclusion

Randomized clinical trials, while traditionally the gold standard of evidence, have several limitations, chief of which is their lack of external validity and consequently a limited ability to impact real-world decision making. Due to recent changes in laws and regulations, including the realization that real-world evidence has an important role to play in informing medical decision making, the pragmatic study design has become an attractive alternative that can address both regulatory and payer needs. Implementing PRTs that a) meet the requirements of regulators and payers, with the ultimate goal of bringing new health technologies to patients quicker and more efficiently, and b) provide the evidence to persuade decision makers to change policies to enable access to those treatments by healthcare providers and their patients is undoubtably a challenge. However, understanding those challenges and how to overcome them through optimizing study design, leveraging existing and comprehensive electronic data stores and technology, and applying data science and operational expertise to generate robust data that demonstrates causal relationship treatment and effect, collectively represent a big step towards making that a reality. ■

For more information, please contact Andrew.Bevan@ppdi.com, Paul.Biedenbach@ppdi.com, or Ariel.Berger@evidera.com.

REFERENCES

1. Government Publishing Office. 21st Century Cures Act. H.R. 34, 114th Congress. 2016. Available at: https://www.gpo.gov/fdsys/pkg/BILLS-114hr34enr/pdf/BILLS-114hr34enr.pdf. Accessed September 5, 2019.
2. US Food and Drug Administration. Framework for FDA's Real-World Evidence Program. December 2018. Available at: https://www.fda.gov/media/120060/download. Accessed September 5, 2019.
3. RE-AIM. Available at: www.RE-AIM.org. Accessed September 5, 2019.
4. Glasgow RE, Vogt TM, Boles SM. Evaluating the Public Health Impact of Health Promotion Interventions: The RE-AIM Framework. *Am J Public Health.* 1999 Sep;89(9):1322–1327. doi:10.2105/ajph.89.9.1322.
5. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 Tool: Designing Trials That Are Fit for Purpose. *BMJ.* 2015 May 8;350:h2147. doi:10.1136/bmj.h2147.
6. ICH. ICH Harmonised Guideline. Estimands and Sensitivity Analysis in Clinical Trials , E9(R1). Current Step 2 Version, Dated 16 June 2017. Available at: www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/E9-R1EWG_Step2_Guideline_2017_0616.pdf. Accessed September 5, 2019.
7. Feltelius N, Gedeborg R, Holm L, Zethelius B. Utility of Registries for Post-Marketing Evaluation of Medicines. A Survey of Swedish Health Care Quality Registries from a Regulatory Perspective. *Ups J Med Sci.* 2017 Jun;122(2):136-147. doi: 10.1080/03009734.2017.1285837. Epub 2017 Mar 3.
8. Erlinge D, Omerovic E, Fröbert O, et al. Bivalirudin versus Heparin Monotherapy in Myocardial Infarction. *N Engl J Med.* 2017 Sep 21;377(12):1132-1142. doi: 10.1056/NEJMoa1706443. Epub 2017 Aug 27.

9. Varas-Lorenzo C, Castellsague J, Stang MR, Tomas L, Aguado J, Perez-Gutthann S. Positive Predictive Value of ICD-9 Codes 410 and 411 in the Identification of Cases of Acute Coronary Syndromes in the Saskatchewan Hospital Automated Database. *Pharmacoepidemiol Drug Saf*. 2008 Aug; 17(8):842-852. doi: 10.1002/pds.1619.

10. Coloma PM, Valkhoff VE, Mazzaglia G, et al. Identification of Acute Myocardial Infarction from Electronic Healthcare Records Using Different Disease Coding Systems: A Validation Study in Three European Countries. *BMJ Open*. 2013 Jun 20;3(6). pii: e002862. doi: 10.1136/bmjopen-2013-002862.

11. Wei WQ, Feng Q, Weeke P, Bush W, Waitara MS, Iwuchukwu OF, Roden DM, Wilke RA, Stein CM, Denny JC. Creation and Validation of an EMR-Based Algorithm for Identifying Major Adverse Cardiac Events while on Statins. *AMIA Jt Summits Transl Sci Proc*. 2014 Apr 7; 2014:112-9. eCollection 2014.

12. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. *N Engl J Med*. 2017 Oct 5; 377(14):1319-1330. doi: 10.1056/NEJMoa1709118. Epub 2017 Aug 27.

13. Berger A, Simpson A, Bhagnani T, Leeper NJ, Murphy B, Nordstrom B, Ting W, Zhao Q, Berger JS. Incidence and Cost of Major Adverse Cardiovascular Events and Major Adverse Limb Events in Patients with Chronic Coronary Artery Disease or Peripheral Artery Disease. *Am J Cardiol*. 2019 Jun 15;123(12):1893-1899. doi: 10.1016/j.amjcard.2019.03.022. Epub 2019 Mar 16.

14. Clinical Trials Arena. PPD and China's HLT to Offer Data Science-Driven Clinical Trial Solutions. 2019 Feb 22. Available at: https://www.clinicaltrialsarena.com/news/ppd-hlt-data-science-driven-clinical-trial-solutions/. Accessed September 5, 2019.

15. US Food and Drug Administration. FDA's Sentinel Initiative. Transforming How We Monitor the Safety of FDA-Regulated Products. Available at: https://www.fda.gov/safety/fdas-sentinel-initiative. Accessed September 5, 2019.

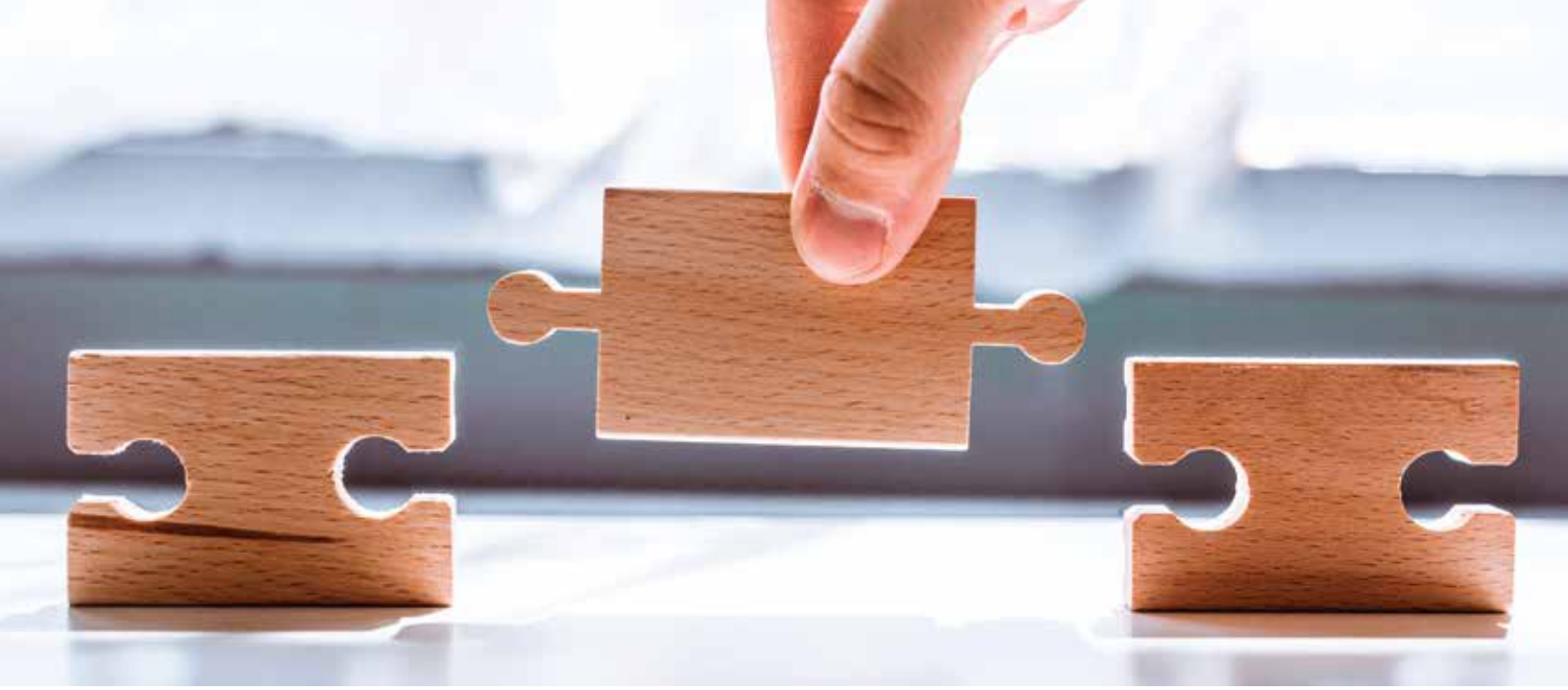
16. Sentinel. Sentinel Common Data Model. Available at: https://www.sentinelinitiative.org/sentinel/data/distributed-database-common-data-model. Accessed September 5, 2019.

17. HL7 FHIR. Available at: www.hl7.org/fhir/. Accessed September 5, 2019.

18. Walinjkar A, Woods J. FHIR Tools for Healthcare Interoperability. *Biomed J Sci Tech Res*. 2018; 9(5).

19. HealthData Management. Slabodkin G. CMS Pilot Taps FHIR to Give Clinicians Access to Claims Data. 2019 Aug 3. Available at: www.healthdatamanagement.com/news/cms-pilot-taps-fhir-to-give-clinicians-access-to-claims-data. Accessed September 5, 2019.

20. Adaptable, The Aspirin Study – A Patient-Centered Trial. Available at: https://theaspirinstudy.org/. Accessed September 5, 2019.



Protocol Design in Real-World Evidence
The Indispensable Link Between Strategic Need and Study Execution

Marielle Bassel, BA
Research Scientist, Real-World Evidence, Evidera

Laura Sayegh, MScA
Research Associate, Real-World Evidence, Evidera

Sofia Fernandes, MSc
Associate Director, Project Management, Real-World Evidence Evidera

Delphine Saragoussi, MD, MScPH
Senior Research Scientist, Real-World Evidence, Evidera

Introduction

The development of new medical treatments follows a well-known pathway from the assessment of safety to the evaluation of therapeutic efficacy, proceeding to pivotal trials to support market authorization decisions.[1] Pivotal trials are most commonly designed as traditional randomized clinical trials, designed to maximize the chance of demonstrating safety and efficacy and often include restrictive inclusion and exclusion criteria. While such trials are well suited for that purpose, they can leave evidence gaps, including:

- How the therapy is most impactfully incorporated into clinical practice where there may be other available treatment options
- Real-world safety and effectiveness in the broader patient groups that may receive the treatment upon authorization but for whom limited information is available from the pivotal studies

As a result, regulatory approval of a new treatment is often followed by post-marketing evaluations aimed at addressing a variety of questions, including understanding the real-world setting of care, disease, safety, efficacy, or effectiveness of therapy.[1] While there are a number of guidelines and articles that focus on details of the key


Marielle Bassel


Laura Sayegh


Sofia Fernandes


Delphine Saragoussi

content of a classic clinical trial protocol, few consider the nuances for protocol design when assessing pre- and post-marketing value in the real-world setting.

Non-interventional studies, used to generate real-world evidence (RWE), complement and provide additional insight to the data produced through clinical trials.[2] Pre-approval designs delineate the natural history and course of disease, standard of care, and contribute to the characterization of burden of illness and unmet needs. Post-approval studies are critical for assessing utilization, treatment patterns, comparative effectiveness and safety, and providing overall value demonstration, as well as informing on important therapeutic findings to help guide treatment decisions and real-world use (See Figure 1).

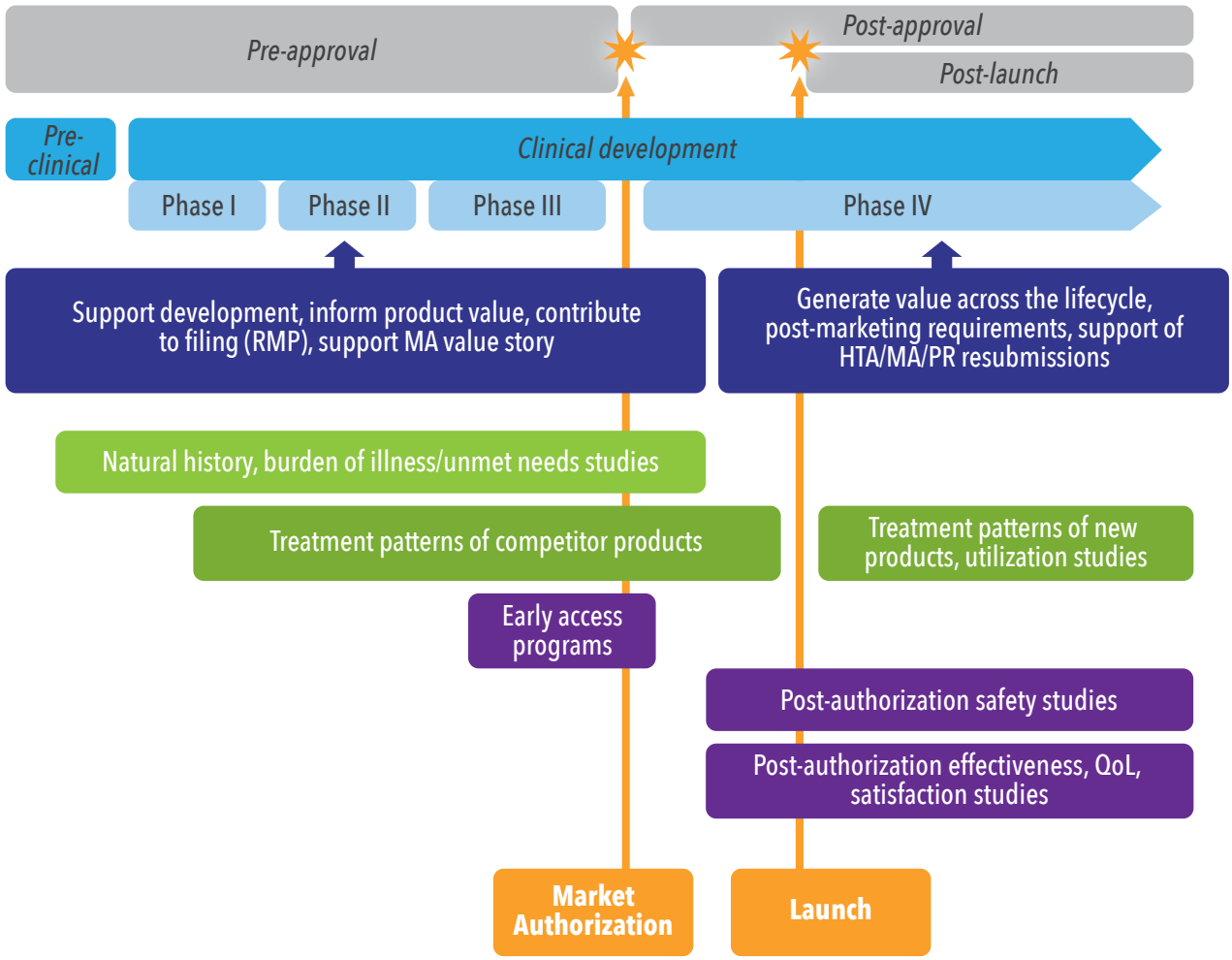
The creation of a study protocol is pivotal in determining the success of the research effort as it is the fundamental document that drives the study, providing pre-defined, standardized procedural methods to effectively communicate plans for study conduct and implementation to all stakeholders and involved parties. Real-world evidence studies differ from clinical trials in nature as they are devoid of any form of intervention. As patient data are gathered and collected during routine clinical care, specific considerations have to be accounted for when developing non-interventional study protocols.

A good protocol should delineate the research questions and outline the research process, show how the design will help achieve the objectives, demonstrate how the study will be operationalized in practice, highlight its feasibility, and convincingly show the importance of the research.

Stakeholder Involvement in Protocol Development

Similar to clinical trials, an invaluable aspect of non-interventional protocol development is the engagement of the sponsor to identify and involve key stakeholders and critical reviewers. Internal stakeholders ensure the full consistency of the study within the company's strategy (See Figure 2). External stakeholders might be end users or approvers of the protocol (See Figure 3). Study type, design, and methods need to be adapted to the research questions and objectives but also to the end users and expected applications of the study results. Factors such as

Figure 1. Objectives of Real-World Evidence across Therapeutic Product Development and Lifecycle



HTA = health technology assessment; MA = market access; PR = pricing and reimbursement; QoL = quality of life; RMP = risk management plan

study type, design, scope, and research questions may also influence the panel of stakeholders and reviewers based on the study needs and research goals. If, for example, a study includes a rare disease population or an orphan drug, there are benefits in engaging patient community and advocacy groups to gain perspective on the feasibility of the objectives and retention strategies.[2] In addition, the conduct of real-world evidence studies requires review by the ethics committees and may be mandated to support regulatory decisions.[3]

Features of an RWE Protocol

Although a real-world study protocol addresses the same principal elements as a clinical trial protocol, there are fundamental differences based on the nature and design of non-interventional studies.[2] The content of these protocols can vary widely according to study objectives and design requirements, nevertheless, there is common content to all non-interventional research protocols, which is presented in Table 1.[4-9]

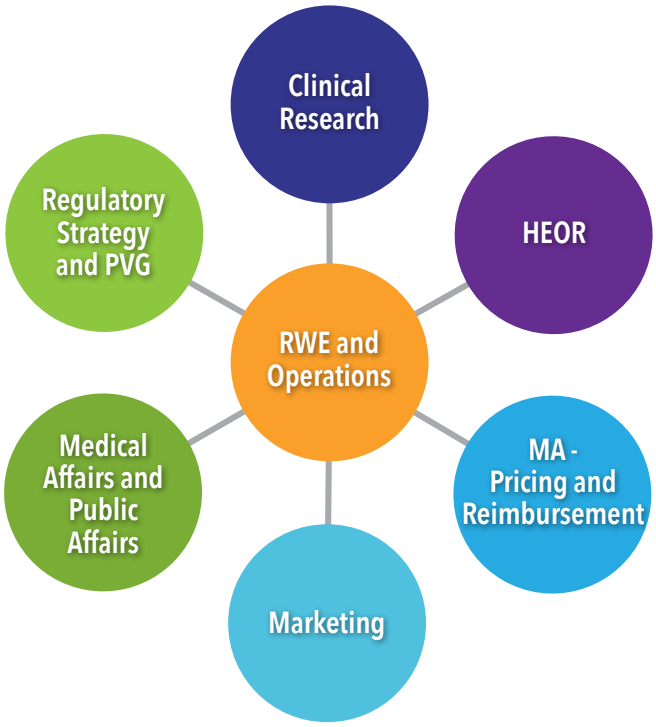
Key Considerations and Challenges of an RWE Protocol

Understanding the underlying rationale behind the sponsor's needs to conduct the study drives the direction and elements of the protocol development (See Figure 4). To ensure successful design and implementation of the study, there are key factors and challenges to consider. Protocols written by trained individuals with appropriate scientific background, as well as knowledge on safety, product strategy, and market access will help to mitigate and address these issues.

> *"The foundation of a successful study is a protocol that is both scientifically sound and operationally viable."*[12]

- With the involvement of diverse stakeholders and multiple interests, it is crucial to incorporate feedback, while **prioritizing input and maintaining focus on the goal** of the study.
- In traditional fixed-design clinical trials, treatment protocols are highly controlled and mandate study visits and adherence to protocol-defined procedures at fixed timepoints.[13] Although this approach ensures satisfactory study conduct in a clinical setting, the same might not be permissible in prospective real-world study protocols, especially in some geographical areas where it is **paramount to avoid protocol requirements that could impact real-world clinical care and routine clinical practice**.
- Addressing real-world outcomes outside of a controlled clinical trial setting requires more flexible data collection. From study design conception, clarity is required in terms of the objectives to permit the **selection of the data** variables necessary to address

Figure 2. Internal Stakeholder Involvement in Protocol Development



HEOR = health economics and outcome research; MA = market access; PVG = pharmacovigilance; RWE = real-world evidence

Figure 3. External Stakeholder Involvement in Protocol Development

HTA = health technology assessment; KOL = key opinion leader

Table 1. Key Protocol Elements

FEATURES	DESCRIPTION
Rationale	• Provides a review of available published and unpublished data • Identifies a clear evidence gap
Study Objectives	• Clearly states the study objective(s), using clear and detailed wording to define the study question(s)

Design, Selection Criteria, Data Source	• **Details**
	  ‣ study design (e.g., cross-sectional, historical, prospective, cohort, case control)
	  ‣ methodology (e.g., site-based, survey, direct to patient, electronic medical record extraction, electronic healthcare database)
	  ‣ type of study (e.g., chart review, prospective, registry)
	  ‣ patient population
	  ‣ number of sites
	  ‣ expected study duration and duration of tasks
	  ‣ study schematic
	  ‣ schedule of events/visits
	• Provides results of any preliminary feasibility assessment
	• Provides considerations for patient recruitment and retention
	• Lists criteria for inclusion and exclusion of potential participants
	• Describes any sources of potential bias
	• Describes the data sources (e.g., electronic medical charts, claims databases, surveys)
	• Clearly defines the outcomes of interest, in priority from primary to exploratory
	• Outlines that any treatment(s) received by the patient during the study is independent of, and therefore not impacted by, the study protocol

Data Collection, Data Management, Quality Control of Data	• Summarizes the data collection method and monitoring plan. For site-based studies, includes measures to optimize site engagement. Highlights expected burden/benefits for sites/patients/caregivers, mentions any incentives/compensations • Describes methods for handling missing data and the process of building that into the data collection tool • Provides an explanation of the procedures ensuring data quality and review
Statistics	• Describes the statistical analysis sets, subgroup or interim analysis, as well as high level detail of planned statistics • Defines the study sample size and precision estimates to achieve the study objective(s)
Ethics, Privacy, and Pharmacovigilance Reporting	• Describes the study related ethical considerations and planned submission for ethics approval • Lists the steps to be taken to protect patient personal data and confidentiality • Details how informed consent is to be obtained (where needed) • Provides criteria for participant withdrawal or discontinuation, and site or study termination • Elaborates the procedures for the collection and reporting of adverse events/adverse drug reactions • Clarifies roles and reporting/publication plans

the study questions and outcomes. A detailed definition of the variables in the protocol will allow identification of any difficulty upfront and facilitate the creation of the case report form, if any.

- **Design and methodological considerations differ depending on the protocol's intended audience**. For example, if the study aim is to provide additional information on post-marketing safety in Europe, then the protocol should adhere to applicable regulatory regulations such as the European Medicines Agency (EMA) Good Pharmacovigilance Practices (GVP) Module VIII,[14] and the EMA Post-Authorisation Safety Studies (PASS),[15] or abide by European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP).[16] These studies may require review and approval from regulatory agencies prior to implementation, and the EMA PASS protocol template or ENCePP protocol checklist[17] may need to be consulted during protocol development.

- Adequate time should be taken to coordinate stakeholder input and accurately review the protocol. Discrepancies can lead to amendments or extension of **study timelines**.[18]

Key Operational Considerations

As the protocol provides all parties involved in a study a reference document for consultation to assist with study implementation, it is expected that downstream study challenges will have been proactively accounted for during development.

The protocol bridges the gap between the research concept and the study conduct.

Clinical trial investigators and sites are not always suitable for non-interventional studies, therefore, it is important to perform outreach concurrent to protocol development to identify the most suitable investigators and sites for study participation, while taking into account marketing authorization, healthcare environment and routine clinical care, geographical features, ethics, data protection, notifications to authorities, and reporting requirements. As data sources exist in various formats and systems in the real world, it is critical to determine the best approach for collecting complete and quality data. Thus, collaboration between the protocol writer and operations allows the integration of relevant study details and realistic assumptions into the protocol during its development.

Summary

While there are challenges and considerations to drafting all study protocols, those designed for real-world studies have additional layers of complexity as they need to be developed in such a way as not to alter real-world routine clinical care patterns. The protocol, derived from the sponsor's strategic needs, must guide and enable the

Recommendations for a Real-World Study Protocol

- Present clear, detailed, and measurable objectives
- Delineate a strong scientific approach that is operationally feasible
- Include description of the variables chosen to estimate the outcomes of interest
- Include potential covariates or confounding factors
- Include ethical and regulatory considerations (in compliance with International Council for Harmonisation [ICH] Good Clinical Practice [GCP][10] and/or Good Pharmacoepidemiology Practice [GPP] guidelines[11])
- Adhere to sponsor standards; comply with internal policies and good documentation practices (GDP)
- Allow for the anticipation of issues and upfront agreements to all study objectives and procedures

Figure 4. Lifecycle of Protocol Development and Study Execution Based on Strategic Need

collection of robust data and the generation of valid results in the highly variable and dynamic real-world setting, irrespective of the study design and data collection method chosen. Successful study execution is bolstered when the protocol writer is an expert in their field, well versed in the numerous methodological and data collection challenges, and supported by a team of scientific and operational experts. This can also be accomplished when the protocol writer, the sponsor, and critical stakeholders engage in early discussions to clearly define the research questions and delineate the conceptual protocol framework, and then continue to keep an open dialogue throughout the process. ■

For more information, please contact Marielle.Bassel@evidera.com, Laura.Sayegh@evidera.com, Sofia.Fernandes@ppdi.com or Delphine.Saragoussi@evidera.com.

REFERENCES

1. Galson S, Simon G. 2016. *Real-World Evidence to Guide the Approval and Use of New Treatments. NAM Perspectives.* Discussion Paper, National Academy of Medicine, Washington, DC. doi: 10.31478/201610b. Available at: https://nam.edu/real-world-evidence-to-guide-the-approval-and-use-of-new-treatments/. Accessed September 4, 2019.
2. US Food and Drug Administration. Guidance for Industry: Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices. 2017. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-real-world-evidence-support-regulatory-decision-making-medical-devices. Accessed July 12, 2019.
3. Kurz X, Perez-Gutthann S, ENCePP Steering Group. Strengthening Standards, Transparency, and Collaboration to Support Medicine Evaluation: Ten Years of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). *Pharmacoepidemiol Drug Saf.* 2018 Mar;27(3):245-252. doi: 10.1002/pds.4381. Epub 2018 Jan 11.
4. Al-Jundi A, Sakka S. Protocol Writing in Clinical Research. *J Clin Diagn Res.* 2016 Nov;10(11):ZE10-ZE13. doi: 10.7860/JCDR/2016/21426.8865. Epub 2016 Nov 1.
5. Biostatistics Group, UCLH/UCL/RFH Biomedical Research Unit. Guidelines for Completing a Research Protocol for Observational Studies 2010. Available at: https://icahn.mssm.edu/files/ISMMS/Assets/Research/IHCDS/Guidelines%20for%20Completing%20a%20research%20protocol%20for%20observational%20studies.pdf. Accessed July 15, 2019.
6. US Food and Drug Administration. Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. 2005. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/good-pharmacovigilance-practices-and-pharmacoepidemiologic-assessment. Accessed August 16, 2019.
7. Government of Canada. Elements of Real World Data/Evidence Quality throughout the Prescription Drug Product Life Cycle. 2019. Available at: https://www.canada.ca/en/services/health/publications/drugs-health-products/real-world-data-evidence-drug-lifecycle-report.html. Accessed July 15, 2019.
8. Hoffmann W, Latza U, Baumeister SE, et al. Guidelines and Recommendations for Ensuring Good Epidemiological Practice (GEP): A Guideline Developed by the German Society for Epidemiology. *Eur J Epidemiol.* 2019 Mar;34(3):301-317. doi: 10.1007/s10654-019-00500-x. Epub 2019 Mar 4.
9. MUHC Research Ethics Board (Neurosciences & Psychiatry). Protocol Drafting Guideline from MUHC RI SOP SOP-CR003-EN04_Appendix 1. 2016. Available at: https://www.mcgill.ca/neuro/files/neuro/protocoledrafingguide_2mar2016.pdf. Accessed July 15, 2019.
10. International Council for Harmonisation of Technical Requirement for Pharmaceuticals for Human Use (ICH). Guideline for Good Clinical Practice. 2016. Available at: https://www.ich.org/home.html. Accessed July 12, 2019.
11. International Society for Pharmacoepidemiology. Guidelines for Good Pharmacoepidemiology Practices (GPP). 2015. Available at: https://www.pharmacoepi.org/resources/policies/guidelines-08027/. Accessed July 23, 2019.
12. International Council for Harmonisation of Technical Requirement for Pharmaceuticals for Human Use. General Considerations for Clinical Studies (Draft). 2019. https://www.ich.org/home.html. Accessed July 30, 2019.
13. US Food and Drug Administration. Framework for FDA's Real-World Evidence Program. 2018. Available at: https://www.fda.gov/media/120060/download. Accessed July 12, 2019.
14. European Medicines Agency. Guideline on Good Pharmacovigilance Practices (GVP). EMA/395730/2012 Rev 2*. 2016. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-viii-addendum-i-requirements-recommendations_en.pdf. Accessed August 16, 2019.
15. European Medicines Agency. Guidance for the Format and Content of the Protocol of Non-Interventional Post-Authorisation Safety Studies (PASS). EMA/623947/2012. 2012. Available at: https://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/10/WC500133174.pdf. Accessed July 12, 2019.
16. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on Methodological Standards in Pharmacoepidemiology (Revision 5). 2010. Available at: http://www.encepp.eu/standards_and_guidances/. Accessed July 16, 2019.
17. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). ENCePP Checklist for Study Protocols (Revision 4), EMA/540136/2009. 2009. Available at: http://www.encepp.eu/standards_and_guidances/checkListProtocols.shtml. Accessed July 16, 2019.
18. Kendle K. Clinical Study Protocols: How to Write to Solve Problems Now and Avoid Big Ones in the Future. *Medical Writing: The Backbone of Clinical Development.* 2017:25-27. Available at: https://www.certara.com/wp-content/uploads/Resources/Articles/AR_ClinicalStudyProtocols.pdf. Accessed September 4, 2019.

Research Operations for Secondary Use of Clinical Sites' EMR

Nicola Sawalhi-Leckenby, MSc
Research Associate, Real-World Evidence, Evidera

Sofia Fernandes, MSc
Associate Director, Project Management, Real-World Evidence Evidera

Vernon Schabert, PhD
Independent Consultant and Former Senior Research Scientist, Evidera

Provisions of the US Food and Drug Administration's 2016 21st Century Cures Act,[1,2] and several initiatives funded by the European Medicines Agency,[3] have greatly increased demand for real-world data (RWD) from life sciences companies. These initiatives have increased the potential for real-world evidence (RWE) derived from RWD to influence regulatory decision making, including approval of new indications for approved drugs. Uses of RWD that get closer to the approval of new indications greatly increase regulators' scrutiny of study design rigor, richness of clinical detail, and validation of data against primary sources.[4] Pre-curated RWD research databases that have been used widely to influence reimbursement or post-authorization decisions have rarely passed the scrutiny demanded for such uses.

Sponsors' pharmacovigilance and medical affairs teams frequently gather RWD directly from medical sites for chart reviews, registries, and other observational studies. These sources have also become more attractive sources for RWD to supplement new indication applications, particularly under accelerated approval schemes for breakthrough therapies and orphan indications.[5-7] The human effort and time investments for such data collection limits sponsors' ability to conduct these studies at scale. However, the


Nicola Sawalhi-Leckenby


Sofia Fernandes


Vernon Schabert

increasing global adoption of electronic medical records (EMRs) at clinical sites has prompted interest in using sites' EMRs systematically for observational studies. The hope of sponsors is that sites can spend less time performing manual abstraction and resolving queries, leading to lower costs, faster data collection, larger sample sizes, and higher quality and accuracy.

Despite the attractiveness of EMR-based site studies, demand for such data frequently outpaces the data exchange technologies required to implement EMR data collection. Technology solutions are possible and are (at least partly) enabled by international data exchange standards implemented in most branded EMRs.[8,9] However, through our experience implementing several EMR data collection studies at clinical sites, we have learned that operational issues can often pose greater barriers to EMR studies than the technology limitations. Stakeholders at clinical sites often lack knowledge and harbor reasonable apprehensions about providing access to EMR data, and their concerns have been amplified as sanctions have increased (and have been more widely publicized) following new privacy laws such as the 2018 European Union (EU) General Data Protection Regulation (GDPR). Implementing site-based EMR studies requires new collaborations and change management within clinical sites, and few have invested in changes to accommodate EMR data collection approaches. Here we present four key lessons for EMR studies that we have gathered through our experience working with sites in multiple countries.

Lesson 1
EMR Studies Operate in a Clinical Trials World

Clinical sites' interest in study participation is commensurate with their direct (and sometimes narrow) perception of benefit. Tangible benefits often outweigh intangible benefits in sites' decisions to participate, particularly given pressures on clinician productivity and revenue generation present in many clinical settings. Transparency regulations ensure that site-based studies offer financial reimbursement commensurate with effort, so site investigators who make purely rational economic decisions would perceive equal effort versus reward between observational studies and RCTs. However, although reimbursement for effort is similar for RCTs and observational studies, investigators often prefer RCTs because of the larger reimbursement potential per study. RCTs also offer investigators access to new investigational product before approval, and greater research prestige relative to observational studies. When we have sent study invitations to experienced study sites, only a third as many sites return the initial Confidential Disclosure Agreement (CDA) for observational studies relative to RCTs.

Because site investigators more frequently opt for participation in RCTs, their institutions have often set up procedures optimized for RCTs but not for observational studies. This has multiple consequences for observational study sponsors. First, site-developed templates for study agreements, ethics applications, and data protection reviews often assume that all studies will be RCTs. When observational study teams plan on secondary use of pseudonymous data, they need to plan on additional time to ask sites how to manage exceptions to an RCT-optimized process. This may include forms that require copies of case report forms (CRFs) that won't exist or a request for adverse event (AE) reporting procedures when no patients will be identifiable for these reports. In a US-based study using a site's custom clinical outcome assessments (COAs) linked to their Epic-brand EMR, we found ourselves educating the sponsored projects office on its requirements under the US Health Insurance Portability and Accountability Act (HIPAA). The office was unaware that because they would be providing us with a "Limited Dataset" under HIPAA, they were required to negotiate a Data Use Agreement (DUA) with us that protected uses of their patient data.

Second, sites' sponsored projects offices and contracting teams often feel less pressure from investigators to sign observational study agreements relative to clinical trial agreements. Observational study teams need to consider this lower motivation when they manage expectations regarding timelines and when developing risk management plans. Even in observational studies, site investigators value positive sponsor engagement, and this can improve a study team's leverage with the site. Encouraging sponsors to plan on additional site engagement time early in the study process can result in more motivated investigators and more efficient site activation.

Lesson 2
It Takes a Village to Judge a Site's EMR Feasibility

Investigator motivation also has considerable impact on feasibility analysis when planning secondary use of sites' EMR data. Researchers must lead feasibility assessments to ensure that 1) clinical data sources are complete and accurate records of relevant patient care, and 2) there is an achievable process to approve and execute the required data exchange. Unlike traditional site-based studies, EMR study feasibility requires coordination of input from site functions such as IT, administrators, sponsored projects offices, data protection, analytics, and legal departments. Site investigators often have little interaction with these functions when providing patient care, and these functions are also often unfamiliar with working together to approve or conduct studies. Therefore, sponsors and their study teams should plan on early and active engagement with multiple site stakeholders to understand whether the site's data and infrastructure will support EMR studies.

To minimize risk of delay and diffusion of responsibility, we recommend that study teams identify a non-investigator site contact who has capacity and desire to coordinate across multiple stakeholders and motivate completion of feasibility responses. Without such a motivated site coordinator, the risk for non-response and delays during

feasibility is substantial. We are currently conducting a pilot of a technology partner's EMR data exchange technology with sites in multiple European countries. We began with 10 interested sites that completed a CDA and began the feasibility process. Of these, only two completed their feasibility questionnaires before we moved on to ethics and data protection reviews. At these two sites, we were able to identify coordinators who committed adequate time to learn an unfamiliar process and convey it to relevant internal stakeholders. At sites where a strong coordinator was not available, our study teams spent substantial time being referred to new site contacts and re-explaining study objectives to staff with little research experience and little relationship with the investigator.

We have also found that early financial reimbursement improves site willingness to support the higher feasibility effort required for EMR studies. In the study we referenced using a site's Epic EMR, we executed a site start-up agreement to cover the feasibility process. This early agreement increased our ease of interaction with the investigator, study coordinators, data protection officer, and analytics team. We had a similar positive experience in a study using EMR data from a clinical site in Norway. Although we needed to negotiate second agreements with each of these sites after receiving all approvals to conduct the study, start-up agreements are best practice to accelerate site activation for studies involving secondary use of a site's data.

Lesson 3
EMR Studies Strain Ethics and Data Protection Workflows

Prior to the availability of EMRs, site-based RWD studies were already employing electronic data collection. Case report forms have long been collected from sites through the use of electronic data capture (EDC) systems. However, compared to data collection from EMRs, site-based studies using EDC rely on human effort to transform source documentation into fit-for-purpose data entries for a study protocol. The human involvement in abstraction and EDC data entry has historically been leveraged to minimize inference and algorithm development by study database programmers, but it has also benefitted studies by further reducing the risk of patient re-identification from study data. Many CRF designers have adopted a set of informally shared practices to accrue these benefits, such as the replacement of specific service dates with date spans and recording of only those services critical to the study database analyses. These CRF design practices usually satisfy ethics bodies' perceptions of low patient identification risk, and they have also limited the amount of technical knowledge ethics reviewers need to approve use of EDCs.

EMR studies hold promise for greater efficiency and scalability because they reduce or eliminate the need for human abstraction. This can only be achieved if raw records pass from the site to the study database programmer, and interpretation effort is shifted from the human abstractor to electronic algorithms applied to raw EMR records. Even if identifiers are removed from raw EMR records before transfer, risk of patient re-identification from pseudonymous EMR data is still higher than from abstracted CRF records. Ethics committees that could previously function without detailed technology competencies must navigate through unfamiliar concepts when evaluating risks and harms in EMR studies.

We have seen substantial variation in the readiness of countries' ethics bodies to handle the challenge of reviewing EMR studies. Ethics bodies in the UK received a head start through development of the Caldicott Principles, originally developed in 1997 (and revised in 2013) following a review of how the NHS handled patient information.[10] By the time the UK implemented GDPR with its Data Protection Act of 2018,[11] the infrastructure to apply Caldicott Principles had long been practiced and was highly consistent with GDPR protections. Research Ethics Committees (RECs) in England and Wales form one of the core functions of the Health Research Authority (HRA), which exists to provide a unified national system for the governance of health research. The HRA is responsible for governing the technological side of EMR data access, which allows RECs to focus on the traditional benefits and harms during study ethics review. The HRA can approve electronic data access through two separate mechanisms – Caldicott Guardians designated at individual sites of care, or a centralized approval known as Section 251.[12]

Evidera has conducted multiple studies with NHS trusts in partnership with CIS Oncology. CIS Oncology's ChemoCare drug ordering platform is also used by many trusts for submissions to the Systemic Anticancer Therapy (SACT) research database. Evidera and CIS Oncology have been able to streamline data collection for site investigators following ethics and data protection approvals, and we have completed analysis of treatments long before they appear in SACT. Caldicott Guardian approvals at NHS trusts can be highly efficient, but processes vary widely by trust. At some trusts, the process appears to have been infrequently used or documented for external study teams, which can lead to long delays and limited feedback before receiving approvals.

In other countries outside the US, it pays to prepare for surprises. As we mentioned above, we are currently piloting a technology partner's EMR data exchange with sites in two European countries. Preliminary discussions with one of the sites in Germany had confirmed that they required ethics approval before the Data Protection Officer (DPO) could review our study request. However, after multiple rounds of review, the ethics committee acknowledged the limits of their competencies to evaluate the data exchange technology. The ethics body instructed our study team to seek advice from the DPO before the ethics committee could issue its opinion. The DPO, once approached, also

deferred a decision until the site's IT department could evaluate. The site's IT department helpfully noted that it could not validate the data exchange technology until the study received ethics and data protection approvals! Study teams who implement site EMR approaches will need to plan for substantial education, coordination, and change management effort to facilitate ethics reviews at participating sites.

Lesson 4
If You've Seen One EMR, You Haven't Seen Them All

The feasibility processes we discussed in Lesson 2 will yield critical information needed to configure data exchange for an approved study. Study teams and sites will need to have thorough alignment on the technical details required to facilitate secure and private data exchange of a site's existing data. However, even the most secure and efficient data exchange can't support study objectives if the desired study data are not where they are expected. In our experience, sponsors and site investigators underestimate the dispersion of sites' data and the heterogeneity of EMR systems. This increases the risk for disappointment when executing an EMR study.

In the Norwegian EMR study mentioned above, our feasibility process showed that clinical data for the patient group of interest was stored in three separate clinical systems. Two of these were separate EMRs, both actively used by the site, but storing different information. EMR A was used to record diagnoses and text notes; it was kept in active use because of its ease for reporting to the Norwegian national patient register. EMR B was made available to the site through a regional partnership, was maintained by an external vendor at little cost to the site, and was used to store prescription and laboratory data. The reliance on an external vendor would add substantial time and cost when integrating EMR B data with EMR A for a clinical study. Fortunately, we also located a third data source, an internal registry managed by site clinicians. Study eligibility criteria required both diagnoses (stored in EMR A) and prescription data (stored in EMR B), but the internal registry permitted site investigators to identify eligible patients more efficiently and simplified the process for requesting supplemental data exports from each of the two EMRs. Site feasibility processes for EMR studies must identify all potential systems that store relevant study data; questions specific to systems used by place of service and by type of data content (e.g., diagnoses, orders, results) can increase the likelihood that multiple systems are identified in feasibility responses.

If this much variation can occur *within* a single site, it follows that variation will also be high *across* sites. Consolidation of EMR market share among US clinical sites offers some hope for consistency of site data, but study teams should not plan on seeing common EMR brands outside of the US. Across our various European EMR studies, we've gathered feasibility data for 20 sites in 11 countries. These 20 sites identified 16 different EMR brands in use. This diversity of implemented EMRs among sites poses significant barriers to efficiency in multi-site EMR studies.

Fortunately, because EMRs are still required to exchange data with other clinical systems, EMR standardization efforts have been underway long before demand increased for site-based RWD. Much of this standardization is accomplished through Health Level Seven (HL7), which has developed EMR data exchange standards since 1987.[8] Virtually all electronic health data systems released to market since the year 2000 support at least one version of HL7 standards; estimates suggest that more than half of the world's healthcare data are exchanged using an HL7 standard.[13] The US Department of Health and Human Services has encouraged adoption of HL7-enabled EMRs through a successive program of legislation[14,15] and rulemaking,[16] including recent initiatives such as Blue Button.[17,18] We hope that US efforts to promote standards-based data exchange will migrate to other countries through market forces. Given the diversity in EMR offerings witnessed globally, study teams cannot rely on developing custom data exchange procedures with each site if they aspire to use site EMR at scale.

Conclusions

Increased adoption of EMR by clinical sites has the potential to transform healthcare not only through better clinical decision making, but also through more efficient clinical research. As we've shown, however, clinical sites, ethics bodies, and data protection officers require substantial education, reassurance, and change management support to be ready for using their EMR data for secondary research.

The history of sponsor-funded clinical trials is relatively short. Drug approvals did not require well-controlled trials until the 1960s,[19] around the same time that human subject protections were formalized in the Declaration of Helsinki.[20] Most clinical sites that now participate in research have developed all their study infrastructure since that time. We trust that sites can and will continue to evolve their readiness and processes as sponsor demand expands to include more EMR use for observational studies.

Despite advancements in EMR technology and its increased adoption, heterogeneity of systems and inconsistent use within healthcare settings pose challenges for the researcher. Study teams need to pay careful attention to vetting sites' use of their systems, including distribution of data across systems and interoperability. These are not things that the traditional site investigator knows well but are discoverable through careful coordination with investigators' colleagues. Site feasibility in the era of EMR studies will involve the broader organization, including both technical and operational stakeholders, beyond the investigator and site coordinator. Site engagement and payment models will need to evolve to ensure efficient and effective EMR studies.

Pursuit of site data for EMR studies will also elevate data privacy concerns for site investigators and their colleagues. Electronic exchange of study data will often pose privacy and security risks comparable to those borne in studies using EDC systems, but sites will need educating and convincing that new procedures come with comparable safeguards. That process of convincing will require engagement with, and buy-in from, more contacts and functions within a site's organization than are required for traditional observational studies. Our experiences engaging sites in these studies give us confidence that revised communication, coordination, and documentation can adequately educate and reassure sites that new paradigms offer comparable protections and the promise of greater efficiency.

Leveraging sites' EMRs for secondary analysis still poses a set of critical technical challenges. Those challenges are magnified by a diverse range of proprietary systems and lagging adoption of data exchange standards. However, we've learned that data exchange technology is actually the last in a series of critical challenges facing the researcher interested in site-based RWD. We encourage sponsors and scientists to consider the human and operational impacts of secondary data use early in the study design phase, and to plan for change management at participating sites until new research models become more widely socialized in the clinical community. ■

For more information, please contact Nicola.Sawalhi-Leckenby@evidera.com, or Sofia.Fernandes@ppdi.com.

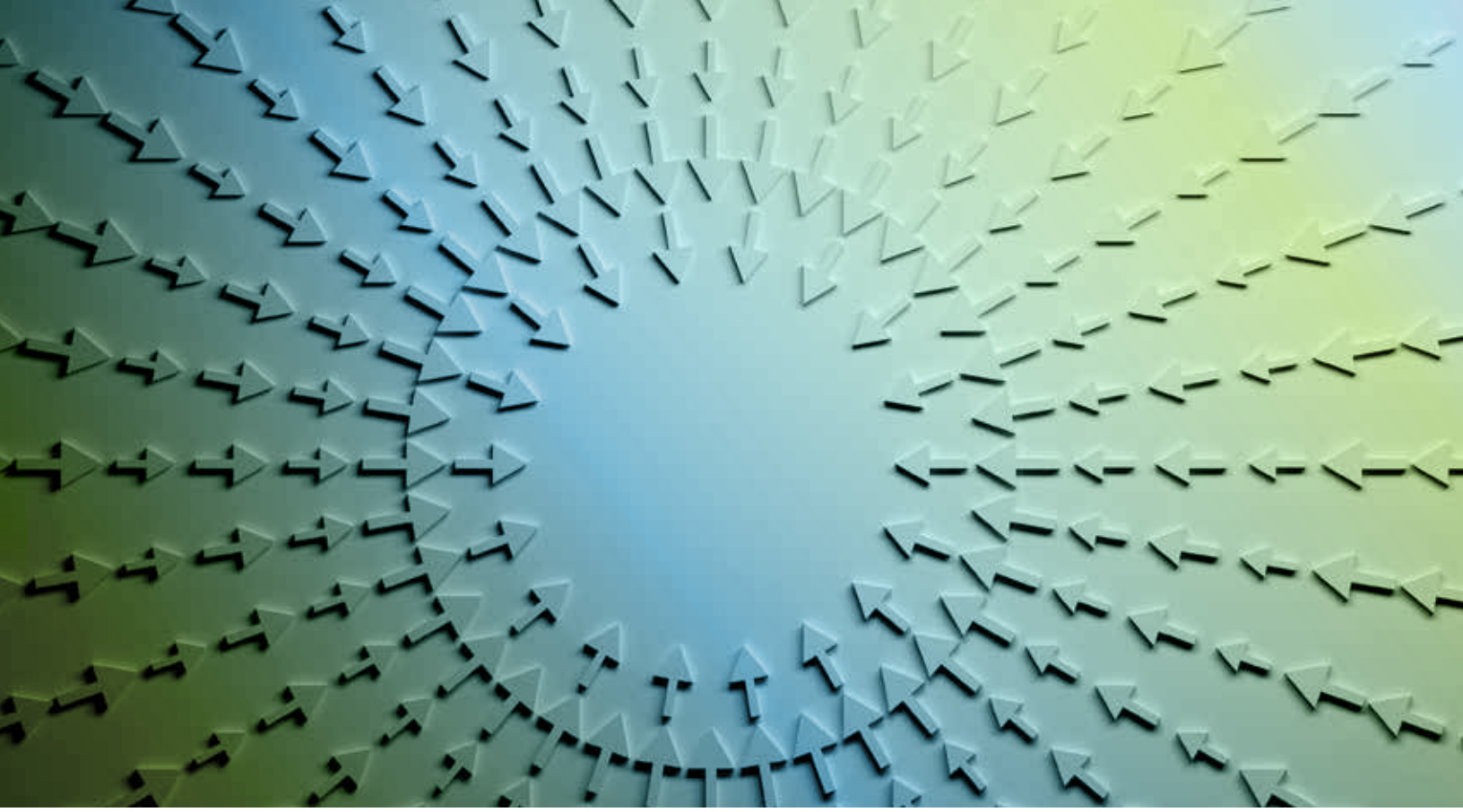
REFERENCES

1. US Food and Drug Administration. 21st Century Cures Act. Available at: https://www.fda.gov/regulatory-information/selected-amendments-fdc-act/21st-century-cures-act. Accessed August 30, 2019.
2. US Food and Drug Administration. Framework for FDA's Real-World Evidence Program. Available at: https://www.fda.gov/media/120060/download. Accessed August 30, 2019.
3. Plueschke K, McGettigan P, Pacurariu A, Kurz X, Cave A. EU-funded Initiatives for Real World Evidence: Descriptive Analysis of Their Characteristics and Relevance for Regulatory Decision-Making. *BMJ Open*. 2018 Jun 14;8(6):e021864.
4. Duke Margolis Center for Health Policy. A Framework for Regulatory Use of Real-World Evidence. September 13, 2017. Available at: https://healthpolicy.duke.edu/sites/default/files/atoms/files/rwe_white_paper_2017.09.06.pdf. Accessed September 4, 2019.
5. European Medicines Agency. PRIME: Priority Medicines. Available at: https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines. Accessed August 30, 2019.
6. European Medicines Agency. Orphan Designation: Overview. Available at: https://www.ema.europa.eu/en/human-regulatory/overview/orphan-designation-overview. Accessed August 30, 2019.
7. US Food and Drug Administration. Breakthrough Therapy Approvals. Available at: https://www.fda.gov/drugs/nda-and-bla-approvals/breakthrough-therapy-approvals. Accessed August 30, 2019.
8. HL7 International. Introduction to HL7 Standards. Available at: http://www.hl7.org/implement/standards/index.cfm?ref=nav. Accessed August 30, 2019.
9. Meehan RA, Mon DT, Kelly KM, et al. Increasing EHR System Usability Through Standards: Conformance Criteria in the HL7 EHR-System Functional Model. *J Biomed Inform*. 2016 Oct;63:169-173. doi: 10.1016/j.jbi.2016.08.015. Epub 2016 Aug 11.
10. NHS. Information Governance Toolkit. Caldicott2 Principles. Available at: https://www.igt.hscic.gov.uk/Caldicott2Principles.aspx. Accessed August 30, 2019.
11. NHS. General Data Protection Regulation (GDPR) -Information. Available at: https://digital.nhs.uk/about-nhs-digital/our-work/keeping-patient-data-safe/gdpr. Accessed August 30, 2019.
12. The United Kingdom Caldicott Guardian Council. Available at: https://www.ukcgc.uk/. Accessed August 30, 2019.
13. HL7 International 2018 Annual Report. Available at: http://www.hl7.org/documentcenter/public_temp_4C4F9EA6-1C23-BA17-0C52E579D74DBB9F/HL7/HL7%202018%20Annual%20Report%20v9.pdf. Accessed August 30, 2019.
14. Schabert VF. Medical Specialty Societies – An Emerging Source of Real-World Evidence. *The Evidence Forum*, October 2016:17-22. Available at: http://www.evidera.com/wp-content/uploads/2017/10/october-2016.pdf. Accessed August 30, 2019.
15. Centers for Medicare and Medicaid Services. Promoting Interoperability (PI). Available at: https://www.cms.gov/Regulations-and-Guidance/Legislation/EHRIncentivePrograms/. Accessed August 30, 2019.
16. HealthIT.gov. Notice of Proposed Rulemaking to Improve the Interoperability of Health Information. Available at: https://www.healthit.gov/topic/laws-regulation-and-policy/notice-proposed-rulemaking-improve-interoperability-health. Accessed August 30, 2019.
17. HealthIT.gov. Blue Button. Available at: https://www.healthit.gov/topic/health-it-initiatives/blue-button. Accessed August 30, 2019.

18. CMS Blue Button 2.0. Available at: https://bluebutton.cms.gov/. Accessed August 30, 2019

19. US Food and Drug Administration. FDA and Clinical Drug Trials: A Short History. Available at: https://www.fda.gov/media/110437/download. Accessed August 30, 2019.

20. World Medical Association. WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. July 9, 2018. Available at: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/. Accessed September 4, 2019.



Enhancing Patient Centricity of HTA
Opportunities in Europe

Carla Dias-Barbosa, MSc
Research Scientist, Patient-Centered Research, Evidera

Asha Hareendran, PhD
Senior Research Leader, Patient-Centered Research, Evidera

Context and Background

Emerging trends for ensuring patient centricity in healthcare decisions by regulators and payers challenge the traditional evidence hierarchy where quantitative research-based knowledge was the strongest evidence, with clinicians' evaluation of outcomes taking precedence over patient reports of their experiences and opinions.[1]

Healthcare decision making systems use health technology assessment (HTA) to inform the reimbursement decisions for new technologies. Health technology assessment is defined as "*the systematic evaluation of the properties and effects of a health technology, addressing the direct and intended effects of this technology, as well as its indirect and unintended consequences, and aimed mainly at informing decision making regarding health technologies. HTA is conducted by interdisciplinary groups that use explicit analytical frameworks drawing on a variety of methods.*[2]"

Appraisals of value conducted by HTA agencies vary in terms of stakeholder involvement, methodology, and processes used, including the evidence base considered and how the results are presented and communicated.[3] Value may be considered in terms of clinical, economic, and patient-relevant outcome improvements, often in the context of societal and ethical considerations.


Carla Dias-Barbosa


Asha Hareendran

There is growing emphasis on the need for more patient-centered methods in the development and evaluation of new technologies. A recent stakeholder survey showed that there was a clear consensus across health technology, industry, and patient representative stakeholders on the importance of promoting patient involvement in HTA at a higher level than currently used, however, there is a need for a more structured process and guidance for patient involvement.[4] While patients are increasingly involved in a range of HTA processes, the findings of another survey conducted among fifteen HTA bodies from twelve countries revealed that only a few HTA organizations evaluate their patient involvement activities.[5] Furthermore, there was some question regarding what constitutes a "meaningful" patient engagement and how it might be assessed, suggesting a desire to move away from less meaningful practices and a need to ensure that the patient involvement approaches taken add value to the process and to the parties involved.[6]

Several HTA agencies and academics associated with HTA are now considering effective ways to incorporate the patients' or, in some cases more generally, the public's perspectives in their methods. The involvement of patients in HTA has been conceptualized in terms of:

1. **Consideration of patient insight (also called patient-based evidence [PBE])** collected through research for evaluating health technologies (e.g., patient experience of symptoms and impacts, perceptions of treatment benefits and risks, expectations, preferences). Patient-based evidence can be produced using qualitative and quantitative primary research, and/or performing secondary research that includes published literature on social and ethical issues.
2. **Patient engagement in the HTA process**, potentially from horizon scanning and early consultations for scientific advice through developing recommendations for evaluating health technologies as individuals or as representatives of associations.

A range of methods and opportunities exist to enhance the patient centricity of appraisals of new technologies (See Table 1). Careful consideration and leveraging of these opportunities throughout the drug and device development continuum can contribute to patient centricity of HTA appraisals to ensure the patient voice is heard when determining access to technologies with benefits for patients.

Various stakeholders are working individually and in consort to develop frameworks and tools to enable patient involvement.[7-10] These initiatives aim to help prepare, engage, and sustain key stakeholders (e.g., patients, assessors, healthcare decision makers) on the inclusion of patient centricity in methods, processes, and communication of HTA appraisal results.

Table 1. Examples of Methods for Patient Involvement in HTA

PATIENT INSIGHT (Patient-Based Evidence)	PATIENT ENGAGEMENT
• Qualitative evidence synthesis	• Informal discussions with patient organizations on an ad-hoc basis
• Qualitative patient interviews and focus groups	• Open Public Consultation where patients, physicians, and members of the public can comment
• Case studies, patient-reported outcomes studies, and surveys	• Formal processes for submission of written information from patient groups and inclusion as part of the considered evidence
• Qualitative interviews within clinical trials to collect patient experience and understand treatment benefit from a patient perspective	• Involvement during early HTA scientific advice to provide input on the design of clinical trials and ensure evidence generated in clinical trials reflects outcomes of importance to patients
• Social media research	• Representation at committee meetings as patient experts to give testimony and answer questions
• Patient preference studies	• Voting rights in appraisal committees

Opportunities to Enhance Patient Centricity of HTA Appraisals

Regulatory agencies, such as the US Food and Drug Administration (FDA), have pushed the patients' voice into the center of drug development and regulatory decisions by launching programs such as the Patient-Focused Drug Development (PFDD) initiative[11] that aims to ensure patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated in drug development and evaluation. The FDA also led efforts to provide guidance about the methods to be used for developing tools to support label claims and for interpreting data based on patient-reported outcome (PRO) measures.[12] More recently the FDA has been open to considering evidence based on qualitative research to ensure the patient perspectives on the value of treatment can be adequately captured using scientific methods.[13]

> ... factors related to patient experience (route of administration, disease burden, impact on caregivers) were only discussed in 11% of HTA appraisals ...

Although the general trend is toward an increased consideration of patient insight in HTA, recent reviews have shown limited examples that illustrate the use of PBE in HTA submissions. A systematic review of HTA submissions (with decisions published after January 1, 2012) to 12 HTA bodies in 7 chronic diseases showed that factors related to patient experience (route of administration, disease burden, impact on caregivers) were only discussed in 11% of HTA appraisals (19/168).[14]

While some HTA assessors tend to consider PBE lower in the evidence hierarchy and have limited impetus to integrate this type of evidence in the evaluation process, a few exceptions do exist as in the examples below.[15]

- Several HTAs produced by the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) incorporated information based on qualitative evidence synthesis of patients' experiences. For example, for the HTA of intervention programs for self-harming, the SBU conducted a systematic literature review of qualitative research studies to understand the experiences and perceptions of people who self-harm with reference to healthcare and school personnel.[16]
- The Scottish Health Technologies Group's (SHTG) HTA of antimicrobial wound dressings in patients with chronic leg ulcers used information about patients' experiences from a literature review, focus groups, and interviews with people in Scotland to formulate conclusions and develop relevant advice. A comprehensive "patient aspects section" based on PBE was developed for the HTA report and this body of evidence was also used to create a patient version of the HTA report.[17]
- The Canadian Agency for Drugs and Technologies in Health (CADTH) used qualitative evidence synthesis for the assessment of interventions for the treatment of obstructive sleep apnea (OSA). This synthesis considered the perspectives and experiences of patients, their family members, and nonmedical caregivers and contributed to the HTA in three major ways: understanding the clinical findings, informing the recommendation generated by the expert committee, and identification of implementation considerations.[18]
- An HTA of tumor necrosis factor (TNF)-alpha inhibitors by the National Institute for Health and Care Excellence (NICE) used evidence from a case study and online survey results provided by a patient group to draft and adjust their recommendations.[19]

There are indeed opportunities for enhancing patient centricity in HTA appraisals through effective patient engagement, increased efficiency of evidence generation and submission, revision of HTA appraisal methods and processes, and effective communication and reporting of HTA appraisals in a manner that is meaningful to all stakeholders.

Effective Patient Engagement in HTA Process

The role of patient representatives has become critical in drug development and HTA appraisals, specifically during early dialogues with regulators and HTA bodies. A review of patient participation in scientific advice procedures since 2007 shows that in nearly every case (93%) patient input provided added value to scientific advice,[20] thus enhancing the need for creating better informed patients.

Resources and education materials exist for patients to understand HTA[21-23] as well as programs to assist patient organizations in setting up patient expert advisory boards, or community advisory boards (CABs), and creating informed patients through education and training to enhance their credibility, legitimacy, and power.[24]

Patient engagement can be particularly valuable in discussions to achieve consensus about relevant outcomes that should be measured and reported in clinical research for evaluation of new technologies. For example, the COMET (Core Outcome Measures in Effectiveness Trials) initiative[25] brings together different stakeholders (including patients/patient advocates, clinicians, researchers, HTA representatives, payers, regulators, and research funders) for the development of agreed upon, standardized sets of outcomes, known as "core outcome sets" (COS) to ensure

drug development focuses on outcomes of relevance to patients, as well as HTA bodies for informed decision making.

Increased Efficiency of Evidence Generation and Submission

Drug manufacturers can play a role in improving the quality and scientific rigour of PBE submitted as part of their HTA submissions, including using PRO tools that measure outcomes that are relevant to patients, and providing clear rationale to show the meaningfulness of results on PRO-based endpoints and which change scores on these tools translate into meaningful benefits and acceptable risks to patients. The use of consistent relevant outcomes, such as the COS discussed earlier, and methods would also improve the ease of understanding and acceptability of PBE.

Additionally, some HTA bodies (e.g., Scottish Medicines Consortium [SMC], NICE, and CADTH) encourage written submissions from patient groups to capture their input about experiences and expectations of new technologies. To share good practices, the HTAi Interest Group for Patient and Citizen Involvement in HTA published *Patient Group Submission Templates* for HTA[26] and provided guidance about the form and type of information that would be useful for an HTA committee.

Using Methods and Processes that Enable Patient Centricity

New tools and methodological frameworks are being created that can be used at various stages of drug development to influence and enhance HTAs, including:

- The methodological framework developed by EUneHTA (HTA Core Model®)[27] for evaluating new technologies and promoting good practices in HTA methods and processes
- The guidance paper for patient involvement in HTA issued by the European Patients' Academy (EUPATI),[21] which lists suggested patient involvement activities for individual HTAs, including:
  - identifying and prioritizing health technology for assessment
  - scoping (developing a framework for an individual HTA)
  - assessing and developing recommendations/ guidelines
  - reviewing and disseminating HTA outcomes[8,21]

Initiatives also focus on the use of patient preference information (PPI) in HTA. The use of PPI in HTA has been relatively limited to date – only two European countries (Germany and Sweden) formally acknowledge the role of PPI in their methods guide and there are examples of PPI being used elsewhere (e.g., England and Wales). However, agencies in various countries (Denmark, England and Wales, Ireland, and the Netherlands) have initiated pilots on the use of PPI, and IMI PREFER[28] is investigating the use of PPI in decision making. More detail on the use of PPI can be found in "Patient Preferences in Health Technology Assessment in Europe: Recent Advances and Future Potential" within this issue of *The Evidence Forum*.

Sustaining Patient Centricity

Communicating the results of HTA appraisal to patients through user-friendly summaries and proactively providing them with feedback about the value of their contribution is essential for improving patient involvement approaches, but also to sustain their engagement in research. For instance, qualitative evidence synthesis of PBE used in HTA appraisals can guide the creation of patient versions of the HTA reports (as seen in the earlier example on antimicrobial wound dressings[17]) and support dissemination of HTA results among patient communities.

The upcoming European Clinical Trial Regulation[29] makes the provision of plain language summaries mandatory for all sponsors conducting interventional clinical trials in the European Union. Under the new regulation, the European Commission will establish a publicly accessible EU database to grant public access to relevant information on clinical trials, including plain language summaries of clinical trial results.

There is an opportunity to ensure that patient centricity in HTA is built into the context of a sustainable partnership with patients with an ethos of respect, sharing, and learning from each other. A successful implementation of this philosophy that could be used as a model is the *British Medical Journal* (BMJ) which introduced editorial changes aimed at making patient partnership integral to the way the journal works and thinks. Additionally, the journal established patient review of all relevant research papers alongside the standard scientific peer review processes. Such initiatives can promote willingness of both patients and the public to participate and engage in research not only as trial participants but as active partners, while also helping to sustain their engagement.

Conclusion and Future Directions

There is an increasing emphasis on providing patient-centered healthcare and ensuring patient involvement in the development and evaluation of new technologies, and several initiatives and examples of successful patient involvement in drug development and HTA currently exist. However, despite growing efforts for patient involvement in HTA around the globe, there is a need for standardization of methods for running patient and public consultation, managing interactions between different stakeholders, developing structured and efficient frameworks, common tools, and best practices across HTA bodies.

In Europe, the European commission proposed a framework for establishing European HTA collaboration and conducting joint clinical assessments (JCAs) at the EU level.[8] Patient involvement is referenced in the JCAs, however, there is a dearth of detail about how such involvement will be operationalized and incorporated in JCAs - and more broadly - in EU HTA. The EU commission proposal for EU HTA offers an exciting opportunity for cross-border cooperation and development and implementation of a common framework for patient involvement in HTA in Europe. Two pivotal areas of patient involvement should be prioritized:

1. Patient engagement in early dialogues to ensure evidence generated in the clinical trials reflects outcomes of relevance to patients
2. Generation and synthesis of robust PBE in a format useful for HTA

Finally, the creation of a multi-stakeholder group within the EU HTA to foster, strengthen, and evaluate patient involvement in EU HTA activities should be a critical path for the inclusion of patients in drug development and HTA in Europe. ■

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For more information, please contact Carla.Dias-Barbosa@evidera.com or Asha.Hareendran@evidera.com.

REFERENCES

1. National Health and Medical Research Council. NHMRC Levels of Evidence and Grades for Recommendations for Developers of Clinical Practice Guidelines. December 2009. Available at: http://citeseerx.ist.psu.edu/viewdoc/download;jsessionid=AEFFDA62A5245D6D07F060B56789ED5A?doi=10.1.1.177.4984&rep=rep1&type=pdf. Accessed September 5, 2019.
2. Health Technology Assessment International. HTA Glossary. Available at: http://htaglossary.net/HomePage. Accessed September 5, 2019.
3. Hutton J, McGrath C, Frybourg JM, Tremblay M, Bramley-Harker E, Henshall C. Framework for Describing and Classifying Decision-Making Systems using Technology Assessment to Determine the Reimbursement of Health Technologies (Fourth Hurdle Systems). *Int J Technol Assess Health Care.* 2006 Winter;22(1):10-8.
4. Boudes M, Robinson P, Bertelsen N, et al. What Do Stakeholders Expect from Patient Engagement: Are These Expectations being Met? *Health Expect.* 2018 Dec;21(6):1035-1045.
5. Weeks L, Polisena J Scott AM, Holtorf AP, Staniszewska S, Facey K. Evaluation of Patient and Public Involvement Initiatives in Health Technology Assessment: A Survey of International Agencies. *Int J Technol Assess Health Care.* 2017 Jan;33(6):715-723. doi: 10.1017/S0266462317000976. Epub 2017 Nov 10.
6. Abelson J. Patient Engagement in Health Technology Assessment: What Constitutes 'Meaningful' and How We Might Get There. *J Health Serv Res Policy.* 2018 Apr;23(2):69-71. doi: 10.1177/1355819618756936. Epub 2018 Feb 7.
7. Patients Active in Research and Dialogues for an Improved Generation of Medicine (PARADIGM). Available at: https://imi-paradigm.eu/. Accessed September 9, 2019.
8. European Network for Health Technology Assessment (EUnetHTA). Available at: https://www.eunethta.eu/about-eunethta/history-of-eunethta/. Accessed September 9, 2019.
9. Community and Patient Preference Research (CaPPRe). Patient Voice Initiative. Available at: https://www.cappre.com.au/PatientVoiceInitiative. Accessed September 9, 2019.
10. Hunter A, Facey K, Thomas V, et al. EUPATI Guidance for Patient Involvement in Medicines Research and Development: Health Technology Assessment. *Front Med (Lausanne).* 2018 Sep 6;5:231. doi: 10.3389/fmed.2018.00231. eCollection 2018.
11. Perfetto EM, Burke L, Oehrlein EM, Epstein RS. Patient-Focused Drug Development: A New Direction for Collaboration. Med Care. 2015 Jan;53(1):9-17. doi: 10.1097/MLR.0000000000000273.
12. US Food and Drug Administration. Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. December 2009. Available at: https://www.fda.gov/media/77832/download. Accessed September 9, 2019.
13. US Food and Drug Administration. Patient-Focused Drug Development: Collecting Comprehensive and Representative Input – Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders. Available at: https://www.fda.gov/media/113653/download. Accessed September 9, 2019.
14. Sarri G, Kenny J, Freitag, et al. PHP315 – How Frequently is Patient Experience Formally Assessed in Health Technology Assessments? Results from A Systematic Literature Review. *Value Health.* October 2018;21(3):S204. doi.org/10.1016/j.jval.2018.09.1209.
15. Single ANV, Facey KM, Livingstone H, Silva AS. Stories of Patient Involvement Impact in Health Technology Assessments: A Discussion Paper. *Int J Technol Assess Health Care.* 2019;35(4):266-272. doi: 10.1017/S0266462319000552. Epub 2019 Jul 24.

16. Swedish Council on Health Technology Assessment. Self-harm: Patients' Experiences and Perceptions of Professional Care and Support [Internet]. Stockholm: Swedish Council on Health Technology Assessment (SBU); 2015 Sep. SBU Alert Report No. 2015-04.

17. NHS Scotland. Patient Information Leaflet. Understanding Your Chronic Wound Dressings, Management and Wound Infection. Available at: https://ewma.org/fileadmin/user_upload/EWMA.org/EWMA_Patient_ressources/Understanding-your-chronic-wound.pdf. Accessed September 9, 2019.

18. CADTH. Interventions for Obstructive Sleep Apnea. February 23, 2016. Available at: https://www.cadth.ca/interventions-obstructive-sleep-apnea. Accessed September 9, 2019.

19. National Institute for Health and Care Excellence (NICE). TNF-alpha Inhibitors for Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthritis. 2016 February 1. Available at: https://www.guidelinecentral.com/summaries/tnf-alpha-inhibitors-for-ankylosing-spondylitis-and-non-radiographic-axial-spondyloarthritis#section-date. Accessed September 9, 2019.

20. EMA. Involvement of Patient Representatives in Scientific Advice Procedures at EMA. Available at: https://www.ema.europa.eu/en/documents/other/involvement-patient-representatives-scientific-advice-procedures-european-medicines-agency_en.pdf. Accessed September 9, 2019.

21. EUPATI. Guidance for Patient Involvement in HTA. Available at: file:///W:\Patient%20Involvement%20in%20HTA\References\EUPATI%20guidance%20for%20patient%20involvement%20in%20HTA.pdf. Accessed September 9, 2019.

22. Health Technology Assessment international (HTAi). Values and Standards for Patient Involvement in HTA. Available at: https://htai.org/interest-groups/pcig/values-and-standards/. Accessed September 9, 2019.

23. Patient Focused Medicines Development. Patient Engagement Industry Training. Available at: https://patientfocusedmedicine.org/patient-engagement-industry-training/. Accessed September 13, 2019.

24. EURORDIS Community Advisory Board (CAB) Programme. Available at: https://www.eurordis.org/content/eurordis-community-advisory-board-cab-programme. Accessed September 9, 2019.

25. COMET Initiative. Available at: http://www.comet-initiative.org/. Accessed September 9, 2019.

26. Health Technology Assessment international (HTAi). For Patient Groups and Individual Patients. Available at: https://htai.org/interest-groups/pcig/resources/for-patients-and-patient-groups/. Accessed September 13, 2019.

27. EUnetHTA. HTA Core Model®. Available at: https://www.eunethta.eu/hta-core-model/. Accessed September 9, 2019.

28. PREFER Patient Preferences. Available at: https://www.imi-prefer.eu/. Accessed August 30, 2019.

29. European Medicines Agency. Human Regulatory: Clinical Trial Regulation. Available at: https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trial-regulation. Accessed September 9, 2019.

Patient Preferences in Health Technology Assessment in Europe

Recent Advances and Future Potential

Kevin Marsh, PhD
Executive Director, Commercial Strategy & New Product Development, Patient-Centered Research, Evidera

Introduction

Healthcare decision making involves value judgements, such as whether the benefits of a treatment outweighs its risks, whether the benefits associated with a therapy are worth its cost, or which patient groups' outcomes should be prioritized for funding. Decision makers are increasingly interested in using quantitative preference data on how stakeholders make such trade-offs to support their decisions. For instance, the US Food and Drug Administration's (FDA) Center for Devices and Radiological Health (CDRH) encourages manufacturers to submit patient preference information (PPI) to support its benefit-risk assessment.[1]

Health technology assessment (HTA) often also involves the use of quantitative preference data, with general population preferences being the basis for the calculation of the tariffs used to estimate utility inputs for the cost-effectiveness analysis.[2] That is, a societal perspective is often adopted. While patient input is sought, often in the form of qualitative insights on the burden of the disease, submissions from patient advocacy groups, or patient representatives being members of decision-making committees,[3] there has traditionally been little or no role in HTA for quantitative PPI.

Recently, however, this has started to change. Across Europe, HTA agencies are consulting on the use of PPI,

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Table 1. Overview of the Use of PPI in European HTA

PREFERENCE METHOD	USE OF PREFERENCE INFORMATION				
	Demonstrate unmet need	Valuing impacts on patients	Trial design	Unclear	Under consultation
Ranking (e.g., SMART exploiting rankings)				Belgium	
Pairwise (e.g., analytical hierarchy process)		Germany		Netherlands	
Choice based (e.g., discrete choice experiment [DCE] or best-worst scaling)	UK	Germany	UK	Hungary Denmark	UK Ireland
Matching (e.g., time trade-off or standard gamble)		Sweden		Czech Republic Netherlands	Ireland
Under consultation					Netherlands Denmark

setting precedents by considering it in their decision making, and providing advice on its use. In some instances, the role of PPI has been formalized in methods guidance. This article provides a snapshot on the use of PPI in Europe and reflects on how its use may change in the future.

The Use of PPI by HTA in Europe

An ongoing ISPOR working group has mapped the use of PPI by HTA agencies in Europe.[4] The mapping involved a literature review; a review of agency websites; a survey of agency staff; and, a consultation with local experts. The results of this review, supplemented by more recent examples of the use of PPI by HTA agencies in Europe, are summarized in Table 1.

The table illustrates how agencies in key markets – in particular Germany, Sweden, and the UK – are leading the use of PPI. In Germany and Sweden, the goal of PPI use has been to base economic evaluation on a more accurate estimate of the value of impacts on patients than would be generated by the QALY. In Germany, the Institute for Quality and Efficiency in Healthcare (IQWiG) has recommended in its method guide that PPI be used to estimate the aggregate benefit in an economic evaluation.[5] In Sweden, it is recommended that PPI be used where the QALY is thought to be inappropriate, such as when valuing changes in short-term pain.

In the UK, PPI has been used by the National Institute for Health and Care Excellence (NICE) in two other ways – in the unmet need section of the submission, demonstrating the value that patients place on finding alternative modes of administration[6]; and to inform the selection of endpoints that are included in a trial. The latter use was the subject of a recent scientific advice offered by NICE on the design of a trial for a COPD treatment. In their press release advertising that they'd provided the scientific advice, NICE stated that it was their aim "to encourage more companies to seek its advice on the development of these studies … so they can be used in the clinical development programs.[7]"

These examples represent the better documented use of PPI in HTA. But the use of PPI may be broader than examples suggest. The ISPOR review reported expert testimony that PPI has been used in reimbursement submissions in Belgium, the Czech Republic, Denmark, Hungary, and the Netherlands.[4] The precise use of PPI wasn't clear from this data.

Ongoing consultations also point to a broadening use of PPI in the future. Pilots and consultation on the use of PPI by HTA agencies were identified by Denmark, Ireland, the Netherlands, and the UK. Exploration of the use of PPI in HTA is also being supported by the Innovative Medicines Initiative's Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle (PREFER) project. Its objective is to generate recommendations on when and how to collect and use PPI to support decision making by industry, regulatory authorities, and HTA bodies.[8] PREFER has established a formal structure to incorporate input from reimbursement agencies into its activities, with representation from agencies from Austria, Belgium, and Germany on its Stakeholder Advisory Group.

Table 2. Challenges and Implications of Using PPI in Reimbursement Decision Making

CATEGORY	CHALLENGE	RESEARCH AGENDA
Conceptual	How are preferences defined?	The need for further clarity on what constitutes PPI is illustrated by the different types of preference data identified in Table 1. Are all these types of data "preferences" or should we only be focusing on a subset of these data? For instance, are choice-based methods, such as DCE, the only source of valid PPI, or do other methods, such as rating the importance of treatment attributes, provide useful PPI? This will depend on how PPI is intended to be used in HTA. For instance, incorporating patient preferences into an economic analysis will require valid trade-off data, while selecting endpoints to include in a trial will only require ranking data. Initiatives such as IMI PREFER will help to define methods and their potential use. Some of the consultation work being undertaken by agencies, such as that in Denmark, will also consider how different types of preference data can contribute to HTA.
Normative	1) Whose preferences should be elicited – treatment-experienced or treatment-naïve patients; patients or patient representatives?	Most of the work currently being funded elicits the preferences directly from patients rather than their representatives, although patient representatives are often involved in the research project as advisors. There are arguments in favor of either treatment-naïve or treatment-experienced patients being the subject of preference research. Treatment-experienced patients have more insight into the attributes included in the design, although they will not necessarily have experienced all of them, as is the case with rare side effects. Furthermore, it is often not always possible to identify a treatment-experienced sample when a study is being undertaken pre-launch. This could be addressed by undertaking the preference study with trial participants, but this introduces a sample bias, as those who opt into trials tend to be more risk tolerant. When consulted, the FDA often recommends that preferences are elicited from both treatment-naïve and treatment-experienced patients.
	2) Should preference focus on patient outcomes, or also process factors such as mode of administration?	Agencies such as NICE explicitly exclude process utility from their reference case. There are, however, examples of process factors informing submissions to NICE, including PPI being used to demonstrate unmet need as a consequence of the mode of administration of current treatments, and general population preferences being used to estimate changes in process utility, which was subsequently included in the economic analysis.[6] As agencies define how they will use PPI, it will be important that they explicitly address the role of process utility.
Methodological	Which preference methods should be adopted?	Initiatives such as IMI PREFER will help to answer this question, however, it is uncontroversial to predict that they will conclude that the appropriate method will depend on the way in which HTA agencies use PPI.
Practical	How can budget, time, and expertise constraints associated with collecting PPI be overcome?	Regulator-quality PPI can be expensive to collect, involving expertise that is currently in short supply. There are important roles for various stakeholders in addressing this challenge. • Academia has a role in providing the training required to boost the capacity to deliver rigorous PPI. • Regulators can provide guidance on when PPI can add value and which methods are appropriate in different circumstances, which will ensure the efficient use of research budgets. • CROs should innovate the way they provide preference research services to improve efficiency.
Procedural	How should PPI be considered alongside clinical or economic evidence?	How can preference studies add to or replace the QALY paradigm? In what stage of HTA should preference studies be utilized? Considering PPI as supportive for HTA is relatively uncontroversial, including demonstrating unmet need, informing trial design, and identifying and quantifying the gaps and uncertainties in economic analyses. Incorporating PPI into economic analysis is more controversial, as most agencies adopt a societal or health service perspective, and thus use general population preferences to value the impacts of treatment. There are exceptions, such as IQWiG, whose use of therapy area-specific efficiency frontiers means that PPI has a clear role in generating aggregate benefit functions.[5] However, for most agencies, incorporating PPI into economic analysis requires further normative work to reconcile patients' preferences with their societal perspective.

Challenges to Incorporating PPI into HTA

Despite the increased interest of HTA agencies, the use of PPI in reimbursement decisions raises a number of issues. Five categories of challenges were identified by a recent review by Huls et al.[9] These are summarized in Table 2 with reflections on the implications for the use of PPI in HTA.

Conclusion

PPI is increasingly used to support regulatory decisions, and sponsors and HTA agencies are actively exploring how this data can also support reimbursement decisions. This latter effort is still in its exploratory phase. A small number of HTA agencies have specified the use of PPI in their methods guidance, but most agency use of PPI is less systematic, either being in the form of novel examples of the use of PPI or at a pilot stage. These case studies and pilots point to the likely increase in the use of PPI for HTA. Where the existing methods fail to capture the value of technologies to patients – e.g., improvements in the mode of administration or health impacts that are not easily captured in the QALY, such as acute pain – PPI has a role to play in HTA. There are issues to be addressed, however, before this role becomes clear. Ongoing initiatives will help provide insight into some of these questions and concerns. In the meantime, sponsors considering the use of PPI are advised to consult agencies on a case-by-case basis to consider its acceptability and likely impact. ■

For more information, please contact Kevin.Marsh@evidera.com.

REFERENCES

1. US Food and Drug Administration. Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling. Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders. August 24, 2016. Available at: https://www.fda.gov/media/92593/download. Accessed September 5, 2019.
2. National Institute for Health and Care Excellence. Guide to the Methods of Technology Appraisal 2013. Process and Methods [PMG9]. April 2013. Available at: https://www.nice.org.uk/process/pmg9/chapter/foreword. Accessed September 5, 2019.
3. Health Technology Assessment International. Good Practice Examples of Patient and Public Involvement in Health Technology Assessment. February 2015. Available at: https://htai.org/wp-content/uploads/2018/02/Good_Practice_Examples_Feb_2015.pdf. Accessed September 5, 2019.
4. ISPOR Stated Preference Special Interest Group. Workshop: Preference Research in HTA Agencies Europe – A Review of Its Use in Approval, Reimbursement and Pricing. Presented at ISPOR Europe 2018, Barcelona, Spain, November 12, 2018.
5. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG). General Methods, Version 5.0 / 10.07.2017: Köln; 2017 Available at: https://www.iqwig.de/download/Allgemeine-Methoden_Version-5-0.pdf. Accessed September 4, 2019.
6. National Institute for Health and Care Excellence (NICE). Technology Appraisal Guidance [TA466]. Baricitinib for Moderate to Severe Rheumatoid Arthritis. 09 August 2017. Available at: https://www.nice.org.uk/guidance/ta466. Accessed September 4, 2019.
7. National Institute for Health and Care Excellence. NICE Provides First Scientific Advice on Patient Preference Study Design. Available at: https://www.nice.org.uk/news/article/nice-provides-first-scientific-advice-on-patient-preference-study-design. Accessed August 30, 2019.
8. PREFER Patient Preferences. Available at: https://www.imi-prefer.eu/. Accessed August 30, 2019.
9. Huls SPI, Whichello CL, van Exel J, Uyl-de Groot CA, de Bekker-Grob EW. What is Next for Patient Preferences in Health Technology Assessment? A Systematic Review of the Challenges. *Value Health*. In Press. Available online 3 August 2019. https://doi.org/10.1016/j.jval.2019.04.1930.

The Growing Need for Real-World Evidence in Medical Devices

Ann Menzie, MS
Senior Director, Evidence Synthesis, Modeling & Communication
Evidera

Medical devices are part of everyday life and essential throughout all areas of healthcare, including prevention, diagnosis, and treatment. They include any device intended for medical purposes, such as instruments, implants, machines, materials, software, etc., and range from tongue depressors and blood pressure cuffs, to cardiac stents and joint replacements, to surgical robots and software. Innovation of medical devices is often an iterative development process based on recognized need rather than transformational improvement to address a unique, unmet clinical need. As a result of the iterative nature of medical device development, little, if any, clinical evidence showing improvement in outcomes is available to support the product launch. Hospitals, ambulatory surgical centers, and physician offices are the primary buyers of medical devices and frequently view them as commodities. Most hospitals have implemented cross-functional value analysis teams to evaluate the clinical and economic impact of adopting new technologies, including medical devices.

The result is a crisis where medical device manufacturers are facing extreme pricing pressure on both new and existing products and are being asked by hospitals to provide evidence to support product claims and value propositions – evidence the manufacturers often do not have. In this environment, there is a significant need for manufacturers to invest in evidence generation to change the discussion with hospitals from price to value.

Unlike the pharmaceutical industry, medical devices often do not require clinical evidence for US Food and Drug Administration (FDA) approval prior to launch. Medical devices are classified by global regulatory authorities using a risk-based classification system: Class I (lowest risk to patients), Class II, and Class III (highest risk to patients). This classification system is used in most global markets and includes four categories (Class I, Class IIa, Class IIb, and Class III). In the US, only 10% of medical devices are classified as Class III and require clinical safety and efficacy data for FDA approval.[1] A summary of these categories is shown in Table 1.

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While hospitals, physicians, and payers request clinical and economic data to inform evidence-based decisions regarding new medical devices, manufactures do not commonly invest in these studies prior to product launch because they have not historically been a requirement for regulatory approval. It is important to note, however, that the regulatory processes are evolving, particularly in the European Union (EU), and new evidence requirements for medical devices are being implemented beginning May 2020.

Manufacturers of medical devices must, therefore, evaluate the impact of investing in post-market clinical trials. While there is often a substantial upside to collecting clinical data on new products, particularly to support claims targeting physicians and hospitals, these studies are costly and time consuming to design and execute. New product innovation is often iterative with new products or line extensions occurring roughly every two to three years. It is not uncommon for the pace of new product launches to exceed the timeline for the clinical trial. Manufacturers must evaluate if the clinical study is worth the investment if the study timeline results in publications reporting outcomes on a previous generation technology.

Medical device companies are leveraging evidence in many ways to maximize their businesses, including driving innovation, supporting evidence-based pricing strategies, and addressing future regulatory evidence requirements. Evidence generation strategies often include a combination of study designs and geographic locations.

Real-world data (RWD) and real-world evidence (RWE) have become integral parts of global evidence generation strategies. RWD refers to data derived from a wide range of sources relating to patient health and healthcare resource utilization,[3] including electronic health records, administrative claims and billing data, patient registries, and mobile devices. RWE is derived from the analysis of RWD and includes clinical evidence reporting usage of a medical device as well as associated benefits or risks.[3] RWE is used to complement post-launch clinical trial data to create a robust evidence base showing safety and efficacy in a defined patient population as well as outcomes in the general population.

Using RWE to Drive Medical Device Innovation

RWE provides a means of revealing markets that are ripe for disruption based on unmet clinical needs. For example, administrative claims databases house de-identified patient data, including medical diagnoses and procedures, prescribed medications, and healthcare costs. Patient cohorts can be identified using procedure or diagnosis codes and their healthcare resource utilization can be tracked longitudinally. Procedures with high rates of

Table 1. Description of Medical Device Categories[1,2]

	Class I	Class IIa	Class IIb	Class III
Description	Minimal potential for harm to the user	Moderate to high risk to the patient and/or user: Medical device used for short term duration (<30 days)	Moderate to high risk to the patient and/or user: Implantable devices and long-term surgically invasive devices (>30 days)	Medical devices that usually sustain or support life, are implanted, or present potential unreasonable risk of illness or injury
% of devices (US)	47%	43%		10%
Examples	Tongue depressors, enema kits	Surgically invasive cannula, infusion pump tubing	Pulmonary stent and valve, nails, and plates	Breast implants, prosthetic heart valves
US Regulatory Path	95% - exempt 5% - 510(k) clearance	510(k) clearance	510(k) clearance (sometimes with clinical evidence)	Pre-market approval (PMA)
Evidence Requirements	Substantial equivalence* for 510(k) clearance often using mechanical testing			Clinical study to collect safety and effectiveness data

*Manufacturers utilize benchtop mechanical testing, such as strength, stability, and wear behavior, to prove substantial equivalence. For some devices, mechanical testing is complemented by cadaveric studies or in vivo data from animal testing and/or cell culture. There are instances where FDA clearance of Class IIb devices will require clinical evidence or a post-market clinical follow-up strategy; however, this is the exception not the norm.

complications and revisions using existing technologies are prime targets for innovation. Additionally, patient subgroups that are at higher risk for adverse events can be identified and targeted for new therapies. RWE analyses are most impactful when coupled with literature searches and clinician feedback to complement the identification of opportunities for innovation that improve patient care.

In addition to using RWE to reveal unmet clinical needs, medical device companies leverage RWD to assess the economic burden of current treatments and identify focus areas for innovation. Providers have a financial interest in reducing the overall cost of care to patients and the healthcare system by adopting technologies that reduce the total cost of care by addressing key economic drivers. These economic drivers may include reducing costly post-operative complications and revisions, time in the Intensive Care Unit (ICU), hospital length of stay, and allowing home discharge status after a surgical procedure compared to more costly alternatives, such as skilled nursing facilities.

Leveraging RWE to Inform Evidence-Based Pricing Strategies

RWE also serves as a key resource for medical device manufacturers for evidence-based pricing of new products. For example, if a medical device is designed to reduce post-operative complications, hospital length of stay, time in the ICU, and/or operating room time, then these opportunities for hospital cost savings should be captured in evidence-based pricing strategies. Manufacturers may leverage hospital administrative databases to assess the cost of the surgical procedure, the length of stay, and cost of revision procedures, and provide insights related to the cost of post-operative care. Understanding where the new product innovation will deliver value to the healthcare system will provide critical inputs into a pricing strategy that succeeds in delivering value to customers while not leaving money on the table for device manufacturers.

Use of RWE to Support Regulatory Requirements for Evidence

Within the US, the FDA has issued guidelines for using RWE from electronic health records, registries, and administrative claims data to support regulatory decision making.[3] This document provides guidance for industry regarding the use of RWE to inform or augment data used to develop the benefit-risk profile provided to the FDA.[3] These data may provide new insights into the usage patterns, performance, and clinical outcomes associated with medical devices and may be used by manufacturers to show compliance with

Table 2. Examples of Surveys and Registries*

Registry	Geography
UK National Joint Registry (NJR)	GB, Wales, Northern Ireland
Endo-Prothesen Register Deutschland (ePRD)	Germany
Dutch Arthroplasty Register (LROI)	Netherlands
Italian Arthroplasty Registry (RIAP)	Italy
European Database on Medical Devices (EUDAMED)	EU
Global Unique Device Identification Database (GUDID)	US
National Evaluation System for health Technology (NEST)	US
Society of Thoracic Surgeons (STS) National Database	US
Vascular Quality Initiative	US
Japanese Percutaneous Coronary Intervention (J-PCI)	Japan
National Cardiovascular Data Registry's Implantable Cardiac Device Registry	US
Canadian Joint Replacement Registry	Canada
National Joint Replacement Registry	Australia

* list not intended to be comprehensive

regulatory requirements.[3] Additionally, RWE will be used in the future to help monitor post-market performance of medical devices. The FDA has developed plans to implement the National Evaluation System for health Technology (NEST), which will utilize RWE to identify safety issues and risks of medical devices used in clinical care.[3] The implementation of NEST is an important step in monitoring medical device safety data and facilitating rapid identification of safety signals that may trigger the need for a device recall. There is a global aim to collect and monitor safety data to protect patients from devices with early failures and other adverse events.

Outside of the US, there is a strong effort to reclassify many surgical implants, such as surgical mesh and spinal implants, from Class II to Class III. In doing so, the evidentiary requirements for regulatory approval will increase substantially. The Medical Device Regulation (MDR) in the EU is a driving force behind this change, and countries such as Australia are considering following suit. RWE will be an important tool in this data collection effort to complement clinical studies to achieve marketing authorization in the EU. MDR will also require robust post-market surveillance (PMS) or post-market clinical follow-up (PMCF) to collect data on safety and performance of the device throughout its entire lifetime.[4] Administrative databases, registries, surveys, and electronic health records will be valuable resources for the PMCF effort that will be required by the new MDR initiative going into effect in May 2020. Table 2 shows examples of surveys and registries from across the globe being utilized to track safety and performance of medical devices.

Considerations for Future Use of RWE

In the future, devices will capture their own data. Implants will have chips that evaluate rate of healing; technologies will monitor for signs of infection; and, wearables will collect ongoing data on gait, movement, and health status. Mobile health apps will collect data on a patient's compliance with hospital discharge instructions and may create a communication channel between the patient and their healthcare team. Medical devices will be tracked throughout their lifetime through unique device identification (UDI), allowing for an even greater degree of device performance and safety analysis. The massive amount of data generated by registries, health apps, and smart devices will create opportunities for companies from other industries to emerge in the medical device space to collect and analyze the data. However, researchers will face challenges to ensure the data analyses are of sound, scientific design and are disseminated in a meaningful way.

In conclusion, this is an exciting time for the medical device industry to harness the power of RWE to drive innovation and support business needs. These data will also be leveraged by payers, hospitals, physicians, and patients to make evidence-based decisions regarding the use of new technology and its value to the healthcare system. With the evolution of evidence requirements for medical devices indicating a greater need for clinical and real-world evidence for both approval and market access, manufacturers are paying more attention to their evidence generation plans for devices and diagnostics, and the benefit could be substantial. ■

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For more information, please contact Ann.Menzie@evidera.com.

REFERENCES

1. U.S. Food and Drug Administration. Learn if a Medical Device Has Been Cleared by FDA for Marketing. December 20, 2017. Available at: https://www.fda.gov/medical-devices/consumers-medical-devices/learn-if-medical-device-has-been-cleared-fda-marketing. Accessed July 19, 2019.
2. European Commission. Medical Devices: Guidance Document - Classification of Medical Devices. MEDDEV 2. 4/1 Rev. 9, June 2010. Available at: http://ec.europa.eu/DocsRoom/documents/10337/attachments/1/translations. Accessed July 19, 2019.
3. U.S. Food and Drug Administration. Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices - Guidance for Industry and Food and Drug Administration Staff. August 2017. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-real-world-evidence-support-regulatory-decision-making-medical-devices. Accessed July 19, 2019.
4. Melvin T, Torre M. New Medical Device Regulations: The Regulator's View. *EFORT Open Rev*. 2019 Jun 3;4(6):351-356. doi: 10.1302/2058-5241.4.180061. eCollection 2019 Jun.

The Growing Influence of the Institute of Clinical and Economic Review on Payer Decisions in the US

Kristin Mickle, MPH
Research Associate, Evidence Synthesis, Modeling & Communication, Evidera

Introduction

Health technology assessment (HTA) bodies, like the National Institute for Health and Care Excellence (NICE) in the UK and the Canadian Agency for Drugs and Technologies in Health (CADTH) in Canada, have become increasingly important in countries across the world as arbiters who determine the reimbursement fate of healthcare interventions in national systems, in addition to ensuring fair access to target populations. For these agencies, such reimbursement decisions are dependent on evidence of clinical efficacy and safety from pivotal clinical trials in the indicated population as well as evidence of cost-effectiveness by means of health economic evaluations. Other bodies like the Institute for Quality and Efficiency in Healthcare (IQWiG) in Germany and the French National Authority for Health (HAS) have a slightly different approach, with economic evaluations considered necessary only after new technologies have demonstrated additional clinical benefit.

Healthcare reimbursement decision-making in the US has historically been an anomaly, given that there is no designated national reimbursement body for the sectored healthcare payer system. In marked contrast to countries with single-payer or national systems for reimbursement, the US healthcare system is fragmented, with myriad payer systems at regional and national levels. US payers also function at individual, group, employer, and government levels and provide varying benefits depending on choice, socioeconomic level, and eligibility. Coverage for and access to prescription drugs or other innovative technologies can vary widely depending on what type of insurance coverage individual patients have. The previously clear difference between the US and other industrialized countries with regards to HTA bodies is becoming increasingly blurred, however, by the role of the Institute for Clinical and Economic Review (ICER), a private research organization founded in 2006 that evaluates the value of emerging healthcare interventions from clinical and health economic perspectives.

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ICER has been receiving widespread attention and is being termed an American "HTA body," serving a purpose like that of NICE and other agencies, with a goal of influencing drug pricing and access decisions.[1] Its primary mission is to enhance the understanding of the value of newly developed health interventions, thus improving health outcomes at a reasonable cost and making fair and equitable access possible. The organization focuses on interventions under evaluation for approval to market by the US Food and Drug Administration (FDA). ICER assessments incorporate information from key players like manufacturers, patient groups, payers, physicians, and clinical experts across the US healthcare system as well as the general public. Since it is an independent organization not affiliated with the government, ICER states that all work for reports are funded by not-for-profit organizations, though other aspects of these activities are funded by manufacturer grants, private insurance companies, and similar groups.[2]

ICER's process of selecting topics for assessment involves public input and market research of the upcoming drug pipeline by an independent analytics group.[3] Based on the recommendations that are made, ICER selects the final list of drugs to be assessed based on key criteria[4] including, but not limited to:

- Presents significantly improved health benefits compared to existing treatment, warranting evaluation of comparative effectiveness
- Anticipates high impact on financial burden to health system or impact on prices of existing treatments
- Expects to receive marketing approval by the FDA within a year
- Impacts policy making or addresses one or more current unmet needs

Historically, most payers in the US have negotiated directly with drug manufacturers. From this perspective, ICER's approach of providing detailed scientific review to encourage wider policy discussions among patient groups, payers, government, and manufacturers could be viewed as a welcome change in the US healthcare system. On the other hand, however, ICER has faced criticism in recent years about its review process, specifically for their approach to economic evaluation of new drugs.[5-7] Such issues have raised a key question within the industry: whether a private organization like ICER can have major influence on reimbursement policies of private and, potentially, public payers, while also ensuring transparency in its process and accountability towards the ultimate consumers – patients.

Why Do ICER Reviews Raise Controversy?

ICER's sudden gain in prominence has caused some concern, and justifiably so.[8,9] A very common criticism centers around the "*value-based price benchmark,*" which ICER considers to be an offering that distinguishes it from other HTA agencies. As part of each evaluation, ICER calculates the benchmark according to the clinical benefit shown in clinical trials and an accompanying cost-effectiveness and budget impact model. The resulting benchmark price is the one at which a drug would be considered cost effective based on a range of recommended cost-effectiveness thresholds ($100,000 to $150,000 per quality adjusted life year [QALY]), which the organization believes reflects a fair price.[10] The benchmark price is based on some assumptions regarding short- and long-term value, as well as actual costs of existing drugs. This price can be controversial because ICER has sometimes suggested large discounts compared to list prices – e.g., as high as 97% for drugs such as inotersen, a treatment indicated for hereditary transthyretin amyloidosis.[11] The drugs at suggested discounts will be cost effective at the corresponding range of cost/QALY thresholds. Some critics also cite that the arbitrary nature of cost-effectiveness thresholds suggests biases in price benchmarks that undervalue new technologies. There has been a lack of national discussion on how to measure the value of life for policy making in the US, and thus there is a reluctance to accept it for decision making despite its prevalent use in other countries. Advocates of cost-effectiveness thresholds maintain that they are meant to merely aid in decision making and have been derived from several assumptions.[12] The cost-effectiveness threshold is supposed to be used as a tool in the appropriate context, not as a single number to make a yes or no decision.

For interventions for rare or ultra-rare diseases, the cost of drug development is extremely high, and companies often aim to have drugs enter the US market at very high list prices to ensure return on investment. HTA bodies usually make special consideration for such drugs to accommodate those interventions that meet an unmet need in a niche, vulnerable population. In some early assessments for rare conditions, ICER failed to do this and received backlash for restricting access to crucial interventions. Based on ongoing feedback from manufacturers and patient groups, ICER updated its value-assessment framework with a special accommodation for ultra-rare conditions (affects <10,000 patients in the US). The adaptation proposes that ICER will test a wider range of cost-effectiveness thresholds in sensitivity analyses of the cost-effectiveness model. They plan to continue using the value-based benchmark price for the range of $100,000 to $150,000 per QALY, but with special considerations made.[13] Such efforts show ICER's amenability to feedback and flexibility to improve their process to better address concerns that are pertinent to the healthcare system.

The timing of ICER evaluations is also controversial. Some of ICER's reports have been considered premature, when FDA decisions are pending and clinical trials still ongoing. These evaluations are commonly initiated, and sometimes completed, while technologies are still under FDA consideration. For this, ICER relies on participation of, and

discussions with, manufacturers during the review process to address potential gaps in clinical evidence. Despite this, skeptics maintain that many ICER evaluations are made public before key clinical evidence is published,[14-16] and so argue that the reports may be biased due to incorrect assumptions based on incomplete data. However, it is important to recognize that, with the growing influence of ICER, manufacturers have been proactively sharing key information with the organization to receive a fair assessment. For instance, in 2017, Sanofi Regeneron shared unpublished clinical trial data on dupilumab with ICER prior to the drug's FDA approval, and the company subsequently accepted the value-based benchmark price when the drug was launched.[17] Other HTA bodies like NICE have also initiated value assessments ahead of marketing approval to help manufacturers prepare their evidence-generation strategies. A notable difference between NICE's strategy and ICER is that the latter also projects the value-based benchmark price, setting up an expected price for the new drug (or even for existing treatments post-entry of new drug) based on assumptions that are not necessarily valid in real-world scenarios post-approval. Payers can then use this as a price-negotiation tool for formulary decisions.[18]

> With the growing influence of ICER, manufacturers have been taking ICER assessments seriously

Currently, the US has no price-control legislation in place, and the influence of economic analyses is less among public payers than private payers. Public payers are mandated to cover FDA-approved treatments and may only consider the safety and efficacy of approved drugs. Private payers, however, may consider these analyses for drug coverage or reimbursement decisions. HTA bodies like NICE and CADTH require data from economic evaluations to be part of reimbursement submissions. The UK National Health Service (NHS) is required to adhere to the recommendations made by NICE. In contrast, ICER provides an independent assessment that any party can choose to use if it suits their decision-making needs. Public and private payers have both collaborated with ICER, including the Veteran's Administration, which worked with ICER on price negotiations to support drug coverage.[19] There is also some evidence of the evolving influence of ICER evaluations on private payers, causing manufacturers to take ICER assessments more seriously.

ICER's influence has been confirmed by small surveys of health plans and payers conducted by independent organizations.[18,20] A two-part survey of decision makers within the Academy of Managed Care Pharmacy (AMCP) eDossier System reported that 58 out of 99 respondents were aware of and had read ICER reports.[21] The evidence from ICER reports was reportedly reviewed by 56% of the survey respondents during the Pharmacy and Therapeutics (P&T) Committee review. Also, 35% of respondents had used the reports to determine affordability; 13% used them as part of price negotiation discussions[21]; and 69% said they used the ICER cost-effectiveness models to inform or validate their own economic models.[21] ICER itself reported high-level findings of a survey of 18 health plans by America's Health Insurance Plans with 100% response rate. Among the findings were that 73% of plans used ICER's reports for review of current and future coverage.[22] Aside from these surveys, there have been more direct examples of the increasing value of ICER reports, including companies using ICER reports as a negotiation tactic for coverage decisions. For instance, the New York Medicaid Program has negotiated discounts for multiple drugs based on recommendations from the New York State Division of Budget to the state's Drug Utilization Review Board.[23] All but one manufacturer provided the necessary rebates to continue coverage for the patients in the state.[24] Similarly, after accepting the value-based benchmark price for dupilumab that was recommended by ICER, Sanofi Regeneron entered into a deal with Express Scripts for alirocumab (indicated for high cholesterol) to gain exclusive formulary placement for the Proprotein convertase subtilisin/kexin type 9 (PCSK9) drug class. Express Scripts will also provide improved access to eligible patients removing stringent requirements for preauthorization for coverage.[25] It should be noted that ICER assessments might be more impactful on discussions with regional health plans than large payer systems who have their own evaluation methods.

Many supporters of ICER see such agreements as success stories for ICER's mission. Negotiations that end with payers adding or retaining drugs on their list of preferred drugs positively impact patient access to new and improved health technologies. Though this process is common in many countries, the considerable opposition may stem from the lack of drug price control in the US. With the growing influence of ICER, manufacturers have been taking ICER assessments seriously since there is a slow trend among some health plans to consider budget impact analyses with the value-based benchmark price while adding new drugs to their formularies. Despite the criticism that ICER has no official responsibility to act as drug price "watchdog," they have advocates who support their efforts to evaluate new health innovations and make efficacious products available to patients at a justifiable value.[26]

Do Methodologies Differ Significantly between ICER and Other HTA Bodies?

Evaluations across ICER, NICE, and CADTH have a similar structure. Each organization completes two main components: (1) a systematic review of literature on the clinical efficacy and safety of the drug, and (2) a health economic evaluation from a payers' perspective using cost-effectiveness and budget impact models. ICER assessments typically have additional components of other benefits/risks, contextual considerations, and budget impact.[27] However, each organization has its own methodology for evaluating

clinical and cost-effectiveness evidence. Well-established, government-mandated HTA bodies like NICE and CADTH review submissions from the manufacturers who are seeking reimbursement. Manufacturers are required to submit a complete assessment including all clinical and economic evidence comparing their own drug to clinically important comparators in the market. The agencies then review the submissions and make recommendations. NICE has an independent Evidence Review Group (ERG) that reviews the company submissions and helps the organization make the final recommendations for reimbursement by the NHS.[28] In contrast, ICER conducts drug value assessments based on its unique methodology, including meta-analyses and economic models.[10,29,30]

ICER develops its own economic model, whereas NICE and CADTH review a model submitted by the manufacturer that is tailored to each respective country's health system.[31-33] With the NICE and CADTH evaluations, the respective review teams critique the manufacturer's model and conduct additional analyses that are necessary for reimbursement decisions. In such circumstances, transparency is exercised through mandated sharing of the manufacturer's modeling code, which review teams can then use to conduct sensitivity analyses to test assumptions that are considered potentially inappropriate. On the other hand, ICER conducts their own sensitivity analyses to test uncertainty associated with model inputs as well as additional inputs recommended by healthcare stakeholders, including manufacturers, patients, and payers.

The conclusions of economic models are restricted by the model assumptions. Sensitivity analyses (deterministic or probabilistic) generally demonstrate the model's sensitivity to uncertainty surrounding particular model inputs. Keeping this under consideration, a model with a perspective that does not truly reflect the assumptions that match a payer's considerations will not be generalizable. Economic models for the UK and Canada are developed from the perspective of the healthcare payer (NHS or Health Canada). These perspectives will therefore truly reflect assumptions that are amenable to the final payer in these countries. ICER also develops its model from the healthcare payer perspective[34] for its base case analyses. However, in the US, there is no single payer to whose perspective the model can be developed, and the characteristics of patients served by different insurance or payer systems vary widely. Hence, individual payers in the US ideally should use the ICER report, in context, and be aware of any assumptions that do not hold true for their target population. If those assumptions have been demonstrated to cause significant uncertainty to the results of the cost-effectiveness analyses, then the incremental cost-effectiveness ratios or value-based benchmark prices should also be viewed in light of those discrepancies. During the assessment of sacubitril/valsartan [Entresto®] (Novartis), there were differences in the inputs that were assessed for the deterministic sensitivity analyses. NICE[35] and CADTH[36] tested one or more basic model parameter variables, like time horizon and discount rate, as well as clinical and cost inputs; ICER focused only on efficacy and cost inputs including, but not limited to, duration of efficacy, risk of cardiovascular mortality, and cost of hospitalization.[37] CADTH and NICE reported a significant impact of time horizon on incremental ratios. CADTH's review committee considered that the model should probably refrain from lifetime or long-term time horizon since there were no long-term clinical data available. Their final recommendations were based on the reduced time horizon. In contrast, ICER made assumptions about long-term benefits and adjusted for duration of efficacy of sacubitril/valsartan to data available from the clinical trial; these results found that the duration significantly impacted the incremental ratios as well. Considering ICER caters to a diverse health system like the US, their assessments should address uncertainty linked to a range of model parameters to satisfactorily demonstrate the uncertainty associated with the incremental cost-effectiveness ratios they present.

ICER also differs in how they present their recommendations based on their evaluations. Since NICE and CADTH are directly answerable to the federal agencies responsible for reimbursement decisions, they make strong final recommendations. They also make recommendations for reimbursement that are subject to certain conditions the manufacturers must meet. Instead, ICER conducts independent assessments that act as a guide for policy-makers and payers; they only present the incremental cost-effectiveness ratios and the value-based benchmark prices to meet thresholds of $100,00 to $150,000 per QALY. The end consumers of the report can interpret the results presented and decide the cost-effectiveness based on their willingness to pay. This approach can be seen as strategic on ICER's part, to avoid making direct recommendations like NICE or CADTH.

How Can Manufacturers Prepare Better for ICER Evaluations?

Manufacturers can leverage ICER's stakeholder engagement processes to collaborate with their researchers and health economists throughout a drug's review. By doing so, companies can provide early input and feedback during the clinical evidence review. Engaging early in the ICER review process can, for instance, provide opportunities for manufacturers to comment on health economic model structures. Some ways of early engagement are as follows.

- Manufacturers who are knowledgeable about available literature that supports key assumptions for economic models can proactively leverage their expertise to advocate for model assumptions that are valid and justifiable.
- Early cost-effectiveness models developed in-house by the manufacturers can help them in engaging with ICER. In this way, they can gauge potential outcomes of the economic evaluations. In addition, identifying potential data gaps for the economic model, putting together

studies to address such data gaps, or alternatively, refining necessary assumptions, can all help in developing a robust economic model.

- Manufacturers can use early insights to help develop approaches to better align product value stories.
- Manufacturers can prepare for pricing negotiations with payers by understanding potential objections and working with those stakeholders to develop appropriate arguments. Companies can also gather opinions and feedback on their evidence-generation strategies from clinical experts and patient focus groups.
- In situations when a negative recommendation or significant price reduction (compared to existing or assumed list price) is a foreseen conclusion, manufacturers can actively involve stakeholders to prepare innovative strategies to avoid conflicts with payers and gain alignment using consistent and sustainable approaches.

Much of the criticism of ICER can be attributed to their evaluation approach still being novel in the US, as well as concerns about transparency and accountability. With the lack of a single healthcare payer system, it is difficult to base decisions on a single assessment. Additionally, due to various priorities of US healthcare system stakeholders, the disapproval ICER receives is often contradictory and hence can be difficult to address. If ICER's role in reimbursement policy keeps expanding, there will be expectations for ICER to adapt their methods to suit the healthcare system better. With some adaptations to their value-assessment framework, ICER has partially addressed certain criticisms and shown an ability to adapt. An overarching market access strategy early in drug development has become crucial with the ever-growing influence of ICER. It serves drug manufacturers well to be amicable partners with the organization in the process of expanding access to crucial health interventions for patients in need, rather than oppose the natural progression of value-based acceptance of new technologies in the US market. ■

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For more information, please contact Kristin.Mickle@evidera.com.

REFERENCES

1. Neumann PJ, Cohen JT, Health Affairs. America's "NICE"? 2018. Available at: https://www.healthaffairs.org/do/10.1377/hblog20180306.837580/full/. Accessed August 22, 2019.
2. Institute for Clinical and Economic Review (ICER) Funding. Available at: https://icer-review.org/about/support/. Accessed August 22, 2019.
3. Institute for Clinical and Economic Review (ICER). How We Do our Work. Available at: https://icer-review.org/methodology/icers-methods/. Accessed August 22, 2019.
4. Institute for Clinical and Economic Review (ICER) Topic Selection. Available at: https://icer-review.org/methodology/icers-methods/topic-selection/. Accessed August 22, 2019.
5. Sagonowski E. *FiercePharma*. Controversial Drug-Cost Watchdog ICER Mulls Changes, and Pharma's Full of Suggestions. 2016. Available at: https://www.fiercepharma.com/pharma/pharma-cost-watchdog-icer-mulls-changes-to-review-process. Accessed August 22, 2019.
6. Sagonowski E. *FiercePharma*. Patient Groups Rebuke CVS on ICER, Saying Cost-Effectiveness Reviews Discriminate. 2018. Available at: https://www.fiercepharma.com/pharma/cost-effectiveness-reviews-are-discriminatory-patient-groups-say-urging-cvs-to-reconsider. Accessed August 22, 2019.
7. Weintraub A. *FiercePharma*. ICER Deems Unapproved Aimmune, DBV Peanut Allergy Drugs Unaffordable, Sparking Backlash. 2019. Available at: https://www.fiercepharma.com/pharma/cost-watchdog-icer-deems-peanut-allergy-drugs-unaffordable-before-they-ve-been-priced. Accessed August 22, 2019.
8. Pagliarulo N. *Biopharma Dive*. PhRMA Criticizes ICER in Latest Skirmish over Valuing Drugs. 2018. Available at: https://www.biopharmadive.com/news/phrma-icer-drug-cost-effectiveness-value-price-feud/524688/. Accessed August 22, 2019.
9. Sagonowski E. *FiercePharma*. Controversial U.S. Cost Watchdog Plans to Expose 'Unsupported' Price Hikes on Old Drugs. 2018. Available at: https://www.fiercepharma.com/icer-plans-annual-report-detailing-price-hikes-old-drugs. Accessed August 22, 2019.
10. Institute for Clinical and Economic Review (ICER). Guide to Understanding Health Technology Assessment (HTA). 2018. Available at: http://icer-review.org/wp-content/uploads/2018/08/ICER-Guide-to-Understanding-Health-Technology-Assessment-6.19.18.pdf. Accessed August 22, 2019.
11. Institute for Clinical and Economic Review (ICER). Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis: Effectiveness and Value: Evidence Report. 2018. Available at: https://icer-review.org/wp-content/uploads/2018/02/ICER_Amyloidosis_Evidence_Report_082918-1.pdf. Accessed August 22, 2019.
12. Bertram MY, Lauer JA, De Joncheere K, et al. Cost-Effectiveness Thresholds: Pros and Cons. *Bull World Health Organ*. 2016 Dec 1;94(12):925-930. Epub 2016 Sep 19.
13. Institute for Clinical and Economic Review (ICER). Modifications to the ICER Value Assessment Framework for Treatments for Ultra-Rare Diseases 2017. Available at: https://icer-review.org/wp-content/uploads/2017/11/ICER-Adaptations-of-Value-Framework-for-Rare-Diseases.pdf. Accessed August 22, 2019.

14. Alnylam. Comments on Draft Scoping Document for ICER's Review of the Treatment of Hereditary Transthyretin-Mediated (hATTR) Amyloidosis. 2018. Available at: https://icer-review.org/wp-content/uploads/2018/02/AmyloidosisDraftScopeComments_04172018.pdf. Accessed August 22, 2019.

15. Amgen. Amgen Response to ICER's Draft Evidence Report and Voting Questions on CAR-T Therapy for B-Cell Cancers. Available at: https://www.amgen.com/media/our-perspective/amgen-response-to-icers-draft-evidence-report-and-voting-questions/. Accessed August 22, 2019.

16. Bristol-Myers Squibb (BMS). BMS Response to ICER's Call for Improvements to its Value Assessment Framework. Available at: https://news.bms.com/sites/bms.newshq.businesswire.com/files/press_release/additional/BMS_Response_to_ICERs_National_Call_for_Improvements_to_its_Value_Framework_9-12-16.pdf. Accessed August 22, 2019.

17. Institute for Clinical and Economic Review (ICER). Dupilumab and Crisaborole for Atopic Dermatitis: Effectiveness and Value. Final Evidence Report and Meeting Summary. 2017. Available at: https://icer-review.org/wp-content/uploads/2016/10/MWCEPAC_ATOPIC_FINAL_EVIDENCE_REPORT_060717.pdf. Accessed August 22, 2019.

18. First Report Managed Care. How Payers Are Using ICER Reports. 2018. Available at: https://www.managedhealthcareconnect.com/article/how-payers-are-using-icer-reports. Accessed August 22, 2019.

19. Institute for Clinical and Economic Review (ICER). The Institute for Clinical and Economic Review to Collaborate with the Department of Veterans Affairs' Pharmacy Benefits Management Services Office. Available at: https://icer-review.org/announcements/va-release/. Accessed August 22, 2019.

20. Schafer J, Galante D, Shafrin J. Value Tools in Managed Care Decision Making: Current Hurdles and Future Opportunities. *J Manag Care Spec Pharm*. 2017 Jun;23(6-a Suppl):S21-S27. doi: 10.18553/jmcp.2017.23.6-a.s21.

21. Lising A, Drummong M, Barry M, Augustovski F. Payers' Use of Independent Reports in Decision Making – Will There Be an ICER Effect? 2017. Available at: https://www.ispor.org/docs/default-source/publications/value-outcomes-spotlight/march-april-2017/vos-payers-use.pdf?sfvrsn=72419413_2. Accessed August 22, 2019.

22. Institute for Clinical and Economic Review (ICER). Survey Highlights Health Plan Use of ICER Reports. 2017. Available at: https://icer-review.org/blog/ahip-survey/. Accessed August 22, 2019.

23. New York State Department of Health, Office of Health Insurance Programs. SFY 18-19: Medicaid Drug Cap Webinar. 2017. Available at: https://www.health.ny.gov/health_care/medicaid/regulations/global_cap/docs/2018-09-17_medicaid_drug_cap.pdf. Accessed August 22, 2019.

24. Thomas K. A Drug Costs $272,000 a Year. Not So Fast, Says New York State. *The New York Times*. 2018. Available at: https://www.nytimes.com/2018/06/24/health/drug-prices-orkambi-new-york.html. Accessed August 22, 2019.

25. Express Scripts. This Is How You Do Value-Based Care. 2018. Available at: http://lab.express-scripts.com/lab/insights/industry-updates/this-is-how-you-do-value-based-care. Accessed August 22, 2019.

26. Butcher L. Can ICER Bring Cost-Effectiveness to Drug Prices? *Manag Care*. 2019 Jun;28(6):30-33.

27. Institute for Clinical and Economic Review (ICER). ICER Value Assessment Framework. Available at: https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/. Accessed August 22, 2019.

28. National Institute for Health and Care Excellence (NICE). Guide to the Methods of Technology Appraisal 2013. Section 5.1 Framework for Estimating Clinical and Cost Effectiveness. Available at: https://www.nice.org.uk/process/pmg9/chapter/the-reference-case#framework-for-estimating-clinical-and-cost-effectiveness. Accessed August 22, 2019.

29. Institute for Clinical and Economic Review (ICER). A Guide to ICER's Methods for Health Technology Assessment. 2018. Available at: http://icer-review.org/wp-content/uploads/2018/08/ICER-HTA-Guide_082018.pdf. Accessed August 23, 2019.

30. Institute for Clinical and Economic Review (ICER). ICER's Reference Case for Economic Evaluations: Principles and Rationale. 2018. Available at: http://icer-review.org/wp-content/uploads/2018/07/ICER_Reference_Case_July-2018.pdf. Accessed August 23, 2019.

31. Canadian Agency for Drugs and Technologies in Health (CADTH). CADTH Common Drug Review. Pharmacoeconomic Review Report: Lumacaftor/Ivacaftor (Orkambi). 2018. Available at: https://cadth.ca/sites/default/files/cdr/pharmacoeconomic/SR0559_Orkambi_PE_Report.pdf. Accessed August 23, 2019.

32. National Institute for Health and Care Excellence (NICE). Technology Appraisal Guidance 398: Lumacaftor–Ivacaftor for Treating Cystic Fibrosis Homozygous for the F508del Mutation. 2016. Available at: https://www.nice.org.uk/guidance/ta398/resources/lumacaftorivacaftor-for-treating-cystic-fibrosis-homozygous-for-the-f508del-mutation-pdf-82602916891333. Accessed August 23, 2019.

33. Institute for Clinical and Economic Review (ICER). Modulator Treatments for Cystic Fibrosis: Effectiveness and Value. Final Evidence Report and Meeting Summary. 2018. Available at: https://icer-review.org/wp-content/uploads/2017/10/CF_Final_Evidence_Report_06082018.pdf. Accessed August 23, 2019.

34. Institute for Clinical and Economic Review (ICER). Overview of the ICER Value Assessment Framework and Update for 2017-2019. Available at: http://icer-review.org/wp-content/uploads/2017/06/ICER-value-assessment-framework-Updated-050818.pdf. Accessed August 23, 2019.

35. National Institute for Health and Care Excellence (NICE). Technology Appraisal Guidance 388: Sacubitril Valsartan for Treating Symptomatic Chronic Heart Failure with Reduced Ejection Fraction. 2016. Available at: https://www.nice.org.uk/guidance/ta388/resources/sacubitril-valsartan-for-treating-symptomatic-chronic-heart-failure-with-reduced-ejection-fraction-pdf-82602856425157. Accessed August 23, 2019.

36. Canadian Agency for Drugs and Technologies in Health (CADTH). CADTH Common Drug Review. Pharmacoeconomic Review Report: sacubitril/valsartan (Entresto). 2015. Available at: https://cadth.ca/sites/default/files/cdr/pharmacoeconomic/SR0447_Entresto_PE_Report.pdf. Accessed August 23, 2019.

37. Institute for Clinical and Economic Review (ICER), California Technology Assessment Forum (CTAF). CardioMEMS™ HF System (St. Jude Medical, Inc.) and Sacubitril/Valsartan (Entresto™, Novartis AG) for Management of Congestive Heart Failure: Effectiveness, Value, and Value-Based Price Benchmarks. Final Report. 2015. Available at: https://icer-review.org/wp-content/uploads/2016/01/CHF_Final_Report_120115.pdf. Accessed August 23, 2019.

Health Economics in China
Changing Pharmaceutical Pricing and Reimbursement

Ying Xiao, MHSA
Research Associate, Evidence Synthesis, Modeling & Communication, Evidera

Ray Gani, PhD
Senior Research Scientist and Senior Director, Evidence Synthesis, Modeling & Communication, Evidera

Krystal Chen, PhD
Consultant, Market Access Consulting, Evidera

Can Chen
Director of Access and HEOR, Happy Life Technology (HLT)

Thitima Kongnakorn, PhD
Senior Research Scientist, Evidence Synthesis, Modeling & Communication, Evidera

Universal healthcare now covers 95% of the population in China and, given limited budgets, healthcare payers are struggling to fund both best medical practice and new innovative medicines. To manage their budgets more effectively, substantial changes have been introduced to the market access process that pharmaceutical companies must follow to achieve reimbursement. Recent critical changes include the introduction of price negotiation and the use of health economics to evaluate the value of new medicines.

These changes present many new challenges for pharmaceutical manufacturers, including the availability of local data, the novel use of health economics, and procedural uncertainties in a fast-changing landscape.

Background

Pharmaceutical companies launching in China aim to have their medicines added to the National Reimbursement Drug List (NRDL). Once on the list, the national basic medical insurance (BMI) covers 50% to 70% of the cost of the medicines. Prior to 2015, this process was haphazard and inconsistent. There were many barriers and uncertainties, which included non-transparent, decision-making processes and long waiting times before listing. Many delays were due to frequent changes in the processes and policy, leaving a significant gap in evaluating new treatments and patchy access with local variation.


Ying Xiao


Ray Gani


Krystal Chen


Can Chen


Thitima Kongnakorn

The national health action plan, "Health China 2030" launched in October 2016, initiated the trend of moving towards evidence-based health policy making in China. The drivers for the trend were identified as[1]:

- Greater life expectancy
- An aging population due to prior demographic policies (e.g., one-child rule) in China, which has resulted in relatively few working-age adults able to provide the elderly care
- Rising incidence of non-communicable disease resulting from rapid urbanization and economic growth[2]
- Expanding healthcare coverage and increasing out-of-pocket payments

These pressures meant that significant reforms and evidence-based policy making were needed to ensure that the provision of healthcare was allocated fairly, consistently, and effectively. This led to the national pilot of price negotiations mainly for innovative but expensive medicines in 2017, transforming the pricing and reimbursement processes in China.

NRDL Updates

The past few years witnessed two major milestones, in 2017 and 2019, in NRLD updates as part of healthcare reform.

2017 NRLD Update: Introduction of Negotiation for Inclusion

In 2017, after a long eight years, the NRDL was updated to add 339 drugs, with a focus on drugs treating catastrophic diseases such as cancer, hematological disorders, and HIV. Products for rare diseases also received more attention than in the past.[3,4]

The total number of covered drugs increased to 2,535, which represents an increase of 15.4% compared to 2009 when the NRDL was last updated. A breakdown of the therapeutic areas of newly listed drugs is shown in Figure 1.[3]

Among the drugs added to the 2017 NRDL, 36 were innovative patent drugs, added after price negotiations with the Ministry of Human Resources and Social Security (MOHRSS) (Note: price negotiation from 2018 onwards has been managed by the National Healthcare Security Administration, NHSA). Of the 36 drugs, 31 were non-TCM (traditional Chinese medicines) drugs including established cancer drugs such as Avastin, Herceptin, Rituxan, and Tarceva.[5,6] To negotiate for inclusion, manufacturers were asked to submit an evidence package that included clinical and safety data, prior sales and sales forecasts, and pricing information. For the first time, pharmaceutical companies were able to include health economic evaluation and budget impact analysis as optional submission materials. However, the exact criteria used for assessment were not clearly defined at the policy level and therefore remained a black box for manufacturers in 2017, and the number of pharmacoeconomic experts was too small for sufficient evaluation during the review process.[7]

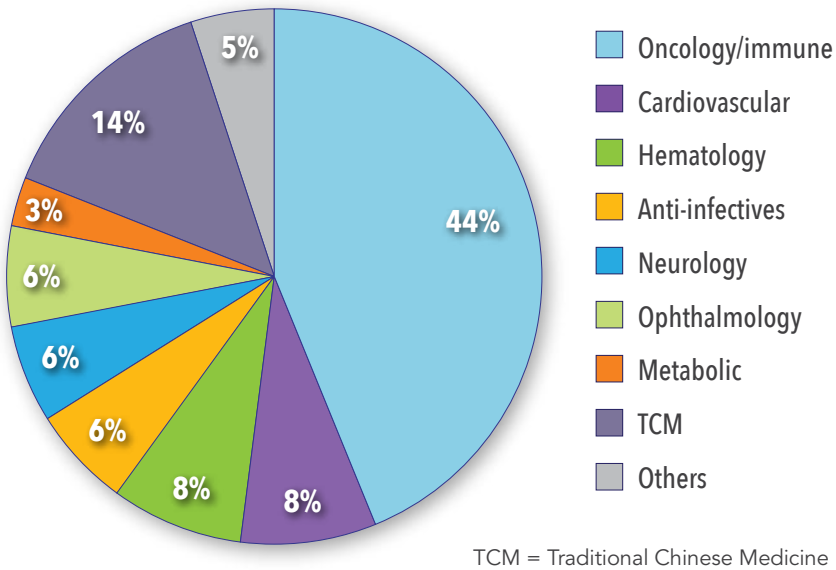
The prices of these drugs were cut by an average of 44% compared to their 2016 average retail prices in exchange for being listed in the NRDL. In late 2018, another 17 cancer drugs went through the same process and agreed on discounts to gain national reimbursement. These included 10 medicines approved after 2017.

Regardless of the price cut, the negotiation and NRDL update in 2017 provided an encouraging signal for market access of innovative medicines in China. In general, inclusion on the NRDL is expected to reduce the financial burden on patients and increase access to these innovative therapies. Although the discounted prices translate into reduced profit margins, the increase in the sales volume of these products is expected to offset the reduction in price. The listed prices of Avastin and Herceptin were cut by 61.4% and 64.8%, respectively, after the 2017 NRDL price negotiations; however, the manufacturer still reported that Chinese growth was the main driver in their overall 8% hike in international sales in 2018.[8]

Further details on the types of drugs that are included in the NRDL, as well as the Provincial Reimbursement Drugs List (PRDL), that are reimbursed by public insurance by reimbursable drug categories[9] are provided in Figure 2.

The process for market access, pricing, and reimbursement for patent drugs in China, developed as part of the 2017 updates,[10] is provided in Figure 3.

Figure 1. Breakdown of Therapeutic Area of Newly Listed Drugs



TCM = Traditional Chinese Medicine

2019 NRDL Update: Role of Health Economic Evaluation

The assessment process for the 2019 NRDL update was announced in April 2019. One of the major changes is the adoption of health technology assessment (HTA) before price negotiation for innovative patent drugs. This update also includes further details on the types of economic analysis that would be required to support the submissions.[11] Outlined below are the key points in this process.

Eligibility

The drugs eligible for inclusion in the 2019 NRDL needed to have been approved by the National Medical Products Administration (NMPA; previously called China Food and Drug Administration [CFDA]) prior to Dec 31, 2018, with priority consideration given to drugs on the essential drug list (EDL) (i.e., drugs for oncology, ultra-rare diseases, chronic diseases, and pediatric illnesses; and emergency medicines).

Figure 2. Drug Coverage by Public Insurance* (Adapted from MOHRSS[3])

National Reimbursement Drug List (NRDL)	Provincial Reimbursement Drug Lists (PRDLs)

• NRDL is separated into two classes
  ▸ Class A: older, generic drugs that are 100% reimbursed by government
  ▸ Class B: premium drugs that are partially reimbursed (50% - 90%)
• Note a separate Essential Drug List (EDL) exists; all EDL drugs are on the NRDL Class A list
	• With reference to the NRDL, local governments have all created PRDLs of their own, which differ in scope (up to 15% adjustment on the NRDL Class B) and the levels of reimbursement offered
	• Drugs can be listed on Provincial lists before they're included on the NRDL, and when they are, this positively influences the decision to include them on the NRDL

*In July 2019, NHSA issued a policy memo[10] that discussed the need for a unified national formulation of the drug reimbursement list. In principle, this new policy removes the authority of provincial governments on making adjustments to the NRDL. Provinces are allowed a three-year 'buffering period' before the regulation is fully implemented.

Evaluation Process

A key step in the assessment for inclusion is the evaluation of clinical necessity (e.g., unmet need), safety profile, clinical effectiveness, and reasonable pricing for drugs with the same indications, following the pharmacoeconomic principle. Innovative patent drugs, with a much higher price or large potential impact on the health insurance budget, may be included pending price negotiation. In July 2019, it was announced that a revised version of the "China Guidelines for Pharmacoeconomic Evaluation, version 2019" will be published around October 2019. Additionally, a formal HTA agency, the National Center for Evaluation of Medicines and Health Technologies (国家药物和卫生技术综合评估中心) was established in October 2018 by the National Health Commission (NHC), with branches to be established in the near future focusing on specific disease areas, such as oncology, cardiovascular disease, and pediatrics. An academic center for HTA research will be selected by the NHSA later this year as well.

Expertise

Experts in four main areas are included throughout the entire assessment process.

- **Advisory experts** (N=300) comment on drug categorization and data analysis, suggest key aspects for technology assessment, and nominate drugs for NRDL inclusion.
- **Selection experts** (N=25,000) referred from academic and industrial perspectives, including clinicians, pharmacists, and medical insurance management experts from all provinces and all levels of healthcare providers (i.e., from primary care clinics to medical centers). From this expert pool, a certain number are randomly chosen to vote for the drugs for NRDL inclusion (i.e., "selected" drug list). Manufacturers of these selected drugs can then submit the application materials, which should include pharmacoeconomic evaluation (mandatory in 2019 for patent drugs). Note that the manufacturers can only submit application materials for the negotiation stage once their drugs are selected.
- **Assessment experts** (N=30) provide recommendations based on cost-effectiveness evaluation and budget impact assessment submitted by the manufacturers, only for innovative patent drugs with a high price and a relatively larger impact on budget among the selected drug list.
- **Negotiation experts** (N=TBD), in conjunction with payers and experts, negotiate directly with manufacturers.

The timeline for the 2019 NRDL assessment process update is shown in Figure 4. The preparation and assessment stages have now been completed and the 2019 updated NRDL was recently published in August 2019.[13]

- 148 drugs have been newly included without negotiation requirement, which brought the total number of drugs on the NRDL to 2,643, with roughly 50% non-TCM drugs. Meanwhile, several drugs were removed from the list due to their limited value in clinical practice or because better alternatives became available.
- In addition, 128 drugs were selected for price negotiation, of which 109 drugs are patent non-TCM

drugs. Along with another 31 patent drugs that were included in the 2017 NRDL and pursuing a deal extension, those selected drugs will enter the negotiation process with the authority.

From 2019 onward, the NRDL will be updated annually with additions and removals of drugs, according to insiders from the authority.[14] This is a significant improvement compared to previous updates which took at least four years and rarely removed drugs from the list. This move has seen many manufacturers start preparing for the 2020 NRDL update.

There will likely be a boost in requests for health economic evaluations to be conducted in China, depending on the results of price negotiation and reimbursement evaluation due to be published in October 2019.

Implications, Evidence-Based Strategies, and Key Challenges

Implications

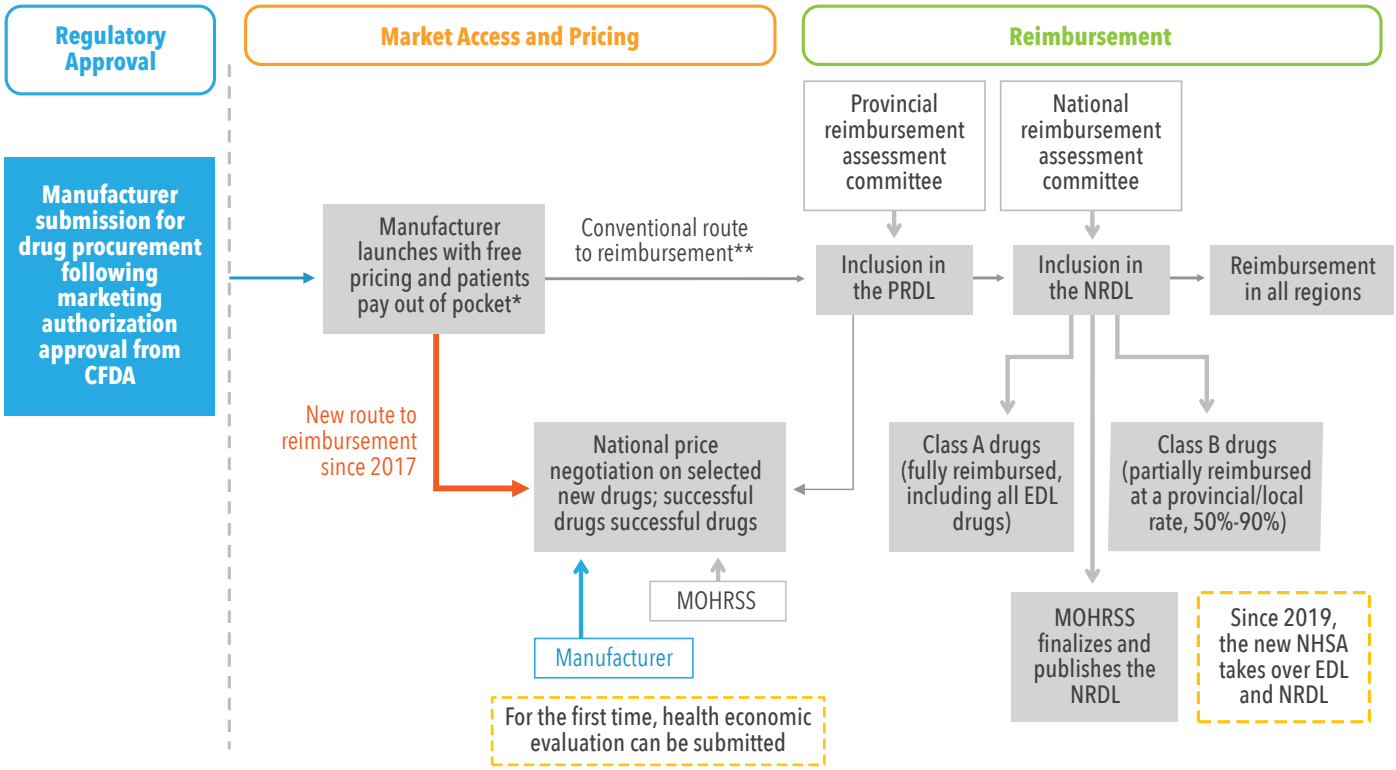
The opportunities for innovative medicines to achieve successful market access and reimbursement have improved and are more predictable than in the past. Established and innovative medicines now have a greater opportunity to quickly reach patients in China. However, the centralized and formalized process means that the NHSA has considerable bargaining power to constrain drug prices and restrict access. As a result, there have been significant price cuts for innovative medicines after price negotiation. The NHSA recently issued a policy memo where a single national formulation of the drug reimbursement list was announced.[14] This means the authority to adjust the reimbursement drug list at the provincial level (i.e., PRDL, see Figure 2) may soon be terminated. Provinces will be given a grace period of up to three years before the regulation is fully executed.

Therefore, it is critical for manufacturers of innovative patent drugs to demonstrate the value of their drugs to get reimbursed at the national level moving forward.

Evidence-Based Strategies for Value Demonstration

With a robust evidence package, manufacturers can bring evidence to light that was previously not transparent in decision making in China. The evidence package for value demonstration should include burden of disease analyses, health economic assessment, and pricing models using local data to support the value story.

Figure 3. Market Access, Pricing, and Reimbursement in China (2017 Updates, Patent Drugs Only)

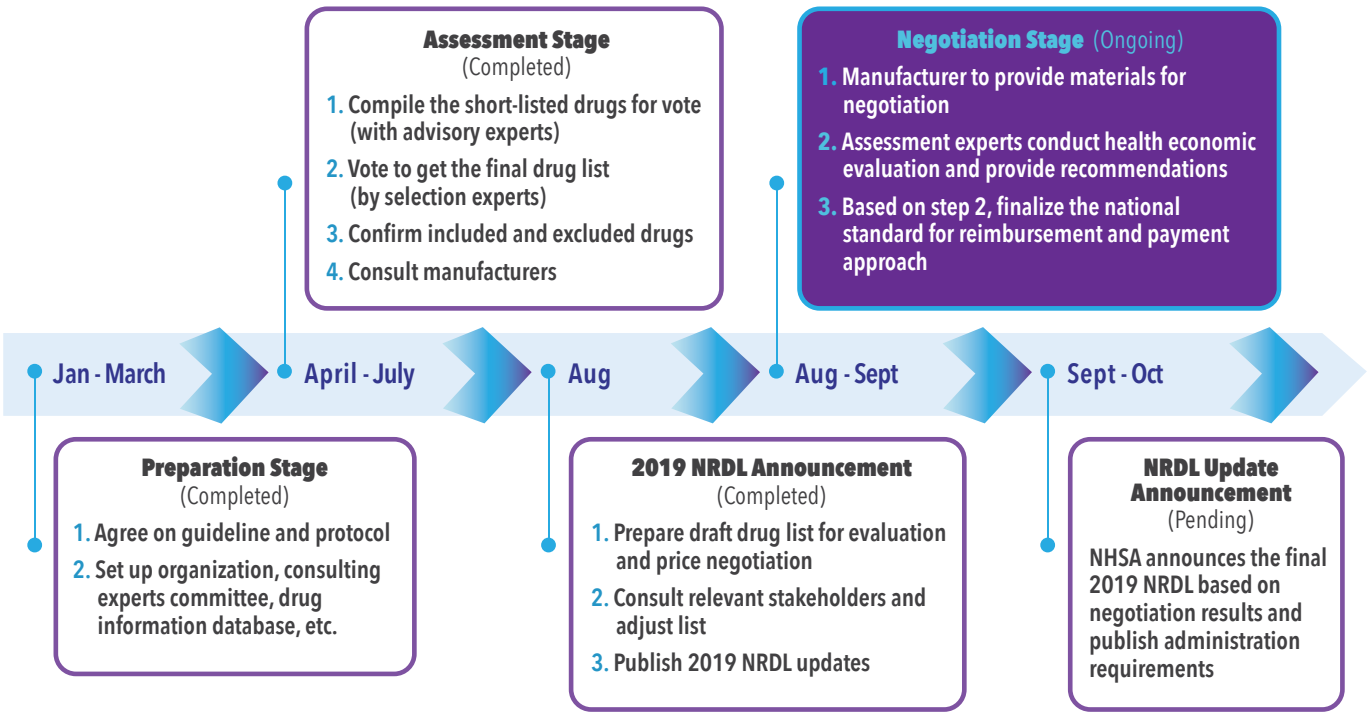


* These drugs are self-financed initially but can be included into the PRDL or local critical disease insurance before the next NRDL update, depending on effectiveness observed in clinical practice.

** The NHSA has issued a policy memo where a single national formulation of drug reimbursement list was announced, which means this conventional route will likely be diminished gradually in the next three years.[14]

CFDA = China Food and Drug Administration; PRDL = Provincial Reimbursement Drug List; NRDL = National Reimbursement Drug List; EDL = Essential Drug List; NHSA = National Healthcare Security Administration, formerly the National Health and Family Planning Commission; MOHRSS = Ministry of Human Resources and Social Security; NDRC = the National Development and Reform Commission; OOP = Out of Pocket

Figure 4. Timeline for 2019 NRDL Update Assessment Process



Proactive Preparation of an Evidence Package

Evidence synthesis and health economic modeling rely on having access to local data, which may take time to collect, so it is vital for pharmaceutical companies to start evidence generation in good time. Important considerations when preparing an evidence package include:

- **Developing a strong value proposition and story** to successfully communicate the value of treatments. Key components should include disease burden, current treatment and unmet need, clinical value, and economic value.
- **Using health economic modeling to generate value evidence package**. This would guide value positioning and pricing strategy, connecting local data capacity with health economic tools. These could include, but are not limited to, disease burden simulation to evaluate unmet medical need, cost-effectiveness analysis to demonstrate value to key opinion leaders and payers, and budget impact analysis for the NRDL.
- **Leveraging local data resources in real-world evidence (RWE) generation**. These studies could focus on disease burden (i.e., including epidemiological study, cost evaluation, and patient research outcomes), treatment patterns, adherence, clinical efficacy, safety, and medical resource utilization. Outcomes from the RWE generation could be used to inform the economic models. Additionally, there are an increasing number of drugs that have been conditionally approved without local clinical trial data, therefore, real-world clinical efficacy and safety data will be required to address the great uncertainties in long-term outcomes.
- **Collaborating with academics in support of HTA review** through evidence generation projects to facilitate the negotiation process.

Targeted Strategy for Market Access and Pricing

While planning for achieving market access approval, as in many other countries, pricing is a strategic exercise that is best navigated with a thorough understanding of the evidence package, the treatment landscape, and local conditions. Meanwhile, different types of patient access schemes (e.g., charity programs, innovative patient assistant programs, response-based payment) would be introduced to offset the burden of high list prices considering affordability, willingness to pay, and competitors' pricing.

Initiating evidence generation at the early stage of drug development could help explore and scope an appropriate indication and product profile to target. Following reimbursement, an evidence development plan could also be explored as a risk-sharing method to mitigate the uncertainty of clinical value and risks of uncontrollable budget impact after inclusion.

Key Challenges

This approach is already well established in other countries using HTA, however, there remain challenges associated with this approach in China. These include:

- **Availability of local data**. Identifying good local data is a challenge as electronic medical records (EMRs), claims databases, and registries are still at an early stage of development and accessibility. Even when data are available from claims and EMRs, they are often not

detailed enough to inform economic models. Charts may contain rich data, but collection relies on time-consuming manual extraction. These data challenges hinder effective development of China-specific models or local adaptation of global health economic models.

- **Resistance to change**. Policy and decision makers are gradually catching up in their knowledge and understanding of health economics and HTA review processes, but since these are methods are still relatively new, there is some resistance to change and a need for continued education.

- **Lack of understanding of health economic methodology**. There is a lack of HEOR experience among industry and academics. Most have been focused on public health policies and few are expert on quantitative analysis, so the talent pool is insufficient to facilitate the fast-growing demand for HTA review.

These challenges emphasize the importance of robust evidence generation, synthesis, communication, and education.

Conclusions

In summary, given the recent healthcare reforms in China as well as changes in the process for NRDL updates, pharmaceutical manufacturers must tailor their market access strategies and should proactively prepare for evidence synthesis and strategic planning to achieve market access and reimbursement in China. Health economic modeling tools, real-world evidence, and collaboration with local data providers and academics will provide support and facilitate value demonstration and effective pricing negotiation of innovative patent drugs. ■

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For more information, please contact Ying.Xiao@evidera.com, Ray.Gani@evidera.com, Krystal.Chen@evidera.com, or Thitima.Kongnakorn@evidera.com.

REFERENCES

1. Tan XD, Liu XX, Shao HY. Healthy China 2030: A Vision for Healthcare. *Value Health Reg Issues*. 2017;12C:112-114.
2. Langenbrunner JC, Marquez PV, Wang S. Toward a Healthy and Harmonious Life in China: Stemming the Rising Tide of Non-Communicable Diseases. Human Development Unit; East Asia and Pacific Region. Washington, DC: World Bank. Available at: http://documents.worldbank.org/curated/en/618431468012000892/Toward-a-healthy-and-harmonious-life-in-China-stemming-the-rising-tide-of-non-communicable-diseases. Accessed July 31, 2019.
3. Ministry of Human Resources and Social Security of the People's Republic of China. Notice of the Ministry of Human Resources and Social Security on Printing and Distributing the National Basic Medical Insurance, Work Injury Insurance and Maternity Insurance Drug List (2017 Edition). Available at: http://www.mohrss.gov.cn/yiliaobxs/YILIAOBXSzhengcewenjian/201702/t20170223_266775.html. Assessed July 31, 2019.
4. www.gov.cn. The New Medical Insurance Drug List is Published with a Focus on Children's Medication and Major Disease Medications. Available at: http://www.gov.cn/xinwen/2017-02/23/content_5170341.htm#1. Assessed July 31, 2019.
5. People.cn. Drug Access for the First Time "National Negotiations" Medical Insurance Directly to the Pharmaceutical Companies "Bargaining". Available at: http://finance.people.com.cn/n1/2017/0807/c1004-29453156.html. Assessed July 31, 2019.
6. Sina. National Medical Insurance Negotiation Work Completed 8 Varieties Out. Available at: http://med.sina.com/article_detail_103_1_30062.html. Assessed July 31, 2019.
7. Koh L, Glaetzer C, Chuen Li S, Zhang M. Health Technology Assessment, International Reference Pricing, and Budget Control Tools from China's Perspective: What Are the Current Developments and Future Considerations? *Value Health Reg Issues*. 2016 May;9:15-21. doi: 10.1016/j.vhri.2015.06.004. Epub 2015 Oct 1.
8. Reuters. Beset by Copies, Roche Gets Sales Boost from China. Available at: https://www.reuters.com/article/us-roche-results/beset-by-copies-roche-gets-sales-boost-from-china-idUSKCN1MR0GQ. Assessed July 31, 2019.
9. Health News. China's Proposed Medical Insurance Treatment List System. Available at: http://www.xinhuanet.com/health/2019-07/24/c_1124790570.htm. Accessed September 10, 2019.
10. Hu J, Mossialos E. China's Drug Pricing and Compensation Policies and Their Effects. *China Health Policy Research*. 2017;20(2):5-15.
11. National Healthcare Security Administration. Announcement of the National Health Insurance Bureau on the Announcement of the Work Plan for the Adjustment of the National Medical Insurance Drug List in 2019. Available at: http://www.nhsa.gov.cn/art/2019/4/17/art_37_1214.html. Accessed July 31, 2019.
12. National Healthcare Security Administration. Notice of the Ministry of Human Resources and Social Security of the State Medical Insurance Bureau on Printing and Distributing the Catalogue of National Basic Medical Insurance, Work Injury Insurance and Maternity Insurance Drugs. Available at: http://www.nhsa.gov.cn/art/2019/8/20/art_37_1666.html. Accessed September 11, 2019.
13. Economic Information Daily. Scientifically Constructing a Dynamic Adjustment Mechanism for National Medical Insurance Catalogues – Medical Insurance Catalog Adjustments Can Benefit More Patients. Available at: http://dz.jjckb.cn/www/pages/webpage2009/html/2019-08/09/content_56222.htm. Accessed September 11, 2019.

Framework for the FDA's Real-World Evidence Program

Introduction and Overview

The 21st Century Cures Act mandated the Food and Drug Administration (FDA) to develop guidance for use of real-world data (RWD) / real-world evidence (RWE) in regulatory decisions.

This framework was released in December 2018 and is intended to support approval of a new indication for an approved drug or biologic, or to help support or satisfy drug post-approval study requirements. (*NOTE: This framework does not apply to medical devices.*)

This new framework will serve as a roadmap for the inclusion of RWD and RWE in regulatory decisions, including standards on how RWD is defined, collected, and analyzed. The FDA will also be providing guidance on study methodologies and designs that meet regulatory requirements in generating evidence of effectiveness, among other topics. (*NOTE: The use of RWD to improve the efficiency of traditional clinical trials is not covered in this guidance.*)

The new framework addresses the following:

- Definition and fitness of RWD for regulatory decision-making
- Study designs with potential to generate scientifically adequate evidence through RWE to support product effectiveness
- Study conduct considerations to ensure regulatory requirements are met

RWE Program Key Considerations

The RWE Program will evaluate the potential use of RWE to support changes to labeling about product effectiveness. Changes include:

- Adding or modifying an indication (e.g., change in dose, dose regimen, or route of administration)
- Adding a new population
- Adding comparative effectiveness or safety information

Simpler, low risk challenges are likely the best and safest situations for considering use of RWE without further guidance in place. Scenarios with substantial safety concerns, such as expanding to pediatric populations, would not be recommended.

A big question will be "what are the regulatory requirements for RWE?"

- Will they differ if using a database vs another data collection approach?
- What about retrospective vs prospective studies?

Again, early discussions with RWE experts and the FDA RWE Program are recommended to inform study development.

FDA's Three-Part Approach to Evaluate Individual Supplemental Applications

1. Whether the RWD are fit for use
2. Whether the RWE study design can provide adequate scientific evidence to answer/help answer the regulatory question
3. Whether the study conduct meets FDA regulatory requirements (e.g., for study monitoring and data collection)

Guidance Development

The RWE program will develop guidance to address:

- Using pragmatic trial elements at every stage of the clinical trial for the development of RWE
- RWD to provide external/historical control arms
- Using observational studies for the generation of RWE

The RWE program will also address regulatory considerations to:

- Evaluate guidance cited for their continued appropriateness to address study designs using RWD to generate RWE
- Finalize guidance on informed consent and collection of data through electronic means under 21 CFR Part 11
- Issue additional guidance as applicable

A more extensive analysis of the framework and what this means for pharmaceutical development can be read at: https://www.evidera.com/wp-content/uploads/2019/04/FDA-RWE-Program-eBook_FINAL.pdf

CADTH Launches Parallel Scientific Advice Programs with NICE and Health Canada

There is growing interest from both regulators and HTA bodies to engage with pharmaceutical and biotech companies earlier in the drug development process to provide insight into the evidence needed to support both regulatory approval and market access. Scientific advice focuses on development strategies and study designs for specific treatments and offers companies the opportunity to ask questions and modify plans based on feedback received, and companies are increasingly seeing the benefit of this advice.

In April 2019, members of Evidera's Policy Trends team had the opportunity to speak with Dr. Amy Sood, Manager, Scientific Advice; and, Dr. Michelle Mujoomdar, Director,

Table 1.

	Standard scientific advice with CADTH only	Parallel scientific advice with NICE-CADTH	Parallel scientific advice with Health Canada-CADTH
Eligibility	Drug products in early-stage development (prior to initiation of Phase III or pivotal trials) including new drugs, existing drugs with new indications, and drugs for rare diseases.		
Briefing book	Manufacturers submit briefing book to CADTH, generally with a maximum of 10 questions for which the manufacturer wishes to obtain advice.	Manufacturers submit same briefing book to each HTA body. Up to two additional, organization-specific questions can be included.	Manufacturers submit same briefing book to each agency/HTA body. A few additional organization-specific questions can be included. Note: Quebec HTA body INESSS is participating in an observer role as it currently does not have a scientific advice program in place.
Meeting	Face-to-face meeting (3 hours) takes place between CADTH and the manufacturer in Ottawa or Toronto, Canada; advice is provided verbally and allows for an open dialogue to discuss key issues identified in the briefing book.	Face-to-face meeting (3 to 4 hours) that is exploratory in nature takes place between CADTH, NICE, and the manufacturer in either England (London or Manchester, dependent on availability) or Ottawa, Canada, based on the manufacturer's choice; key issues identified in the briefing book are discussed.	Face-to-face meeting (3 hours) takes place between CADTH, Health Canada, and the manufacturer in Ottawa, Canada; advice is provided verbally and allows for an open dialogue to discuss key issues identified in the briefing book. While INESSS attends the meeting, it is not providing advice at this time.
Interaction between and within agencies	There are various time points (both before and after the face-to-face meeting) when the organization/organizations meet to discuss issues and where alignment in advice can occur, while respecting the roles and remits of each organization.		
Advice report	Manufacturer receives written record of scientific advice from CADTH.	Manufacturer receives separate advice reports from CADTH and NICE as well as a joint summary from the two HTA bodies highlighting areas of alignment.	Manufacturer receives separate advice reports from CADTH and Health Canada.
	In all three programs there is an optional process for the manufacturer to submit clarification questions on the advice reports; the responses from the organizations are in writing.		
Expert involvement	CADTH aims to engage one clinical expert, one CADTH expert, and one health economic expert (if relevant). Experts attend the face-to-face meeting in person.	Experts are engaged separately by CADTH and NICE. Experts attend the face-to-face meeting in person or via teleconference, depending on the location.	CADTH engages up to three experts who attend the face-to-face meeting in person.
Patient involvement	Conducted by CADTH.	Conducted separately by CADTH and NICE.	Conducted by CADTH.
Fees	Fees charged by CADTH based on the complexity and scope of briefing book.	Fees charged by both HTA bodies based on the complexity and scope of briefing book.	Service follows CADTH's fee schedule based on complexity and scope of briefing book, as Health Canada is not currently charging.
How many completed?	Program has been running since January 2015. As of March 2019, 14 CADTH-only services have been completed.	Program has completed one pilot parallel scientific advice service.	Program has not yet received any applications.

CADTH=Canadian Agency for Drugs and Technologies in Health | HTA=health technology assessment
INESSS=Institut national d'excellence en santé et services sociaux | NICE=National Institute for Health and Care Excellence

Scientific Affairs, with the Canadian Agency for Drugs and Technologies in Health (CADTH). Their discussion centered on new scientific advice opportunities available through CADTH, specifically two new parallel scientific advice programs with the National Institute for Health and Care Excellence (NICE) and Health Canada, and addressed issues such as:

- What new opportunities for scientific advice now exist with CADTH
- What the processes are for obtaining advice through these new programs
- Why CADTH is collaborating with NICE
- How CADTH's scientific advice program differs from others

An overview of CADTH's scientific advice programs can be seen in Table 1.

The full interview can be accessed at: https://www.evidera.com/policy-trends-update-cadth-launches-parallel-scientific-advice-programs-with-nice-and-health-canada/.

Insights from the NICE 2019 Annual Conference on Transforming Care

In May 2019, the National Institute for Health and Care Excellence (NICE) held its annual meeting, 'NICE 2019: Transforming Care', celebrating 20 years of its commitment to healthcare. The meeting brought together stakeholders across the life sciences, health technology, and digital sectors to discuss NICE's role in the delivery of high quality, fully -integrated, patient -centered guidance.

Evidera sent several representatives to garner insight into NICE's perspective on improving access to innovative treatments and what it means for our clients. A synopsis of our impressions from the meeting are included here, and a more detailed overview of the most important highlights from the conference is available on our website: https://www.evidera.com/wp-content/uploads/2019/06/2019-09-NICE-recap-FINAL.pdf.

Over the last 20 years, the role and scope of NICE has grown significantly. Today, NICE is one of the international leaders in health technology assessment (HTA) standards and processes, and an increasing number of companies across the life sciences industry are engaging with the organization for technical and strategic support.

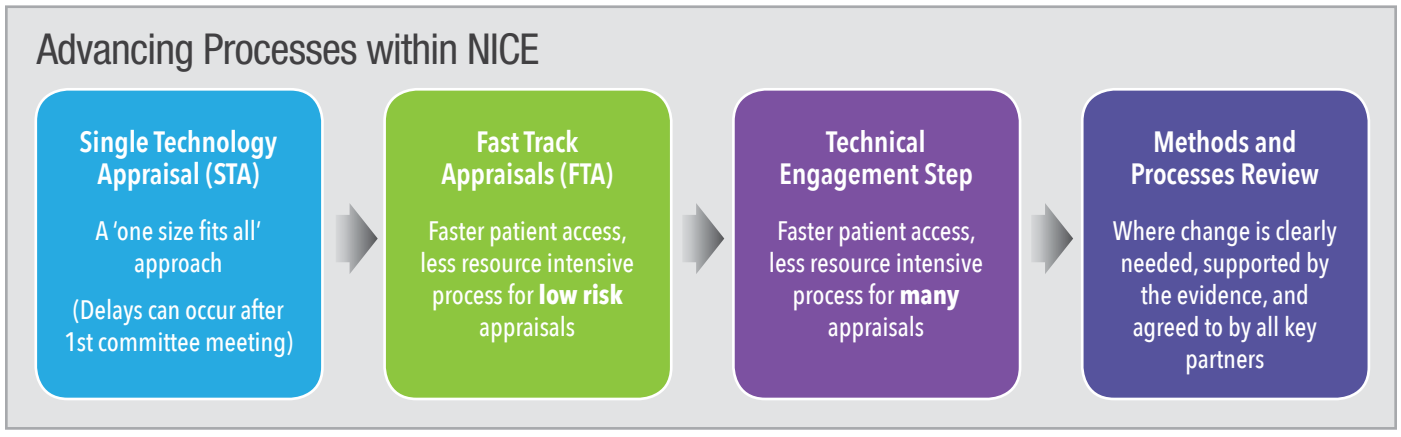
During the day-long meeting, NICE updated stakeholders on the following key themes.

Early Engagement - Evolution and Expansion of Early Engagement through Scientific Advice

A common theme throughout the meeting was the benefit of early involvement of NICE in the drug development process to allow better alignment of evidence needs for both regulatory approval and market access.

NICE Scientific Advice (NSA) aims to provide detailed guidance to companies on prospective clinical and economic evidence generation plans, enabling companies to develop an evidence base that clearly demonstrates the value of their product. Recently, NSA has provided advice relating to patient preference studies. Key insights from independent clinical and academic experts are involved in the process, as well as National Health Service (NHS) decision makers and patient advocates.

NSA is now also providing Preliminary Independent Model Advice (PRIMA) – a new health economics model advice service. While the NSA currently provides companies with advice on the design and structure of economic models at the conceptual stage of the development process, PRIMA offers an advanced level of service via an external peer review of models. The PRIMA team systematically inspects the model and provides a detailed report of model enhancement recommendations for consideration.



NICE has established or is working on collaborations with several bodies, such as:

- NSA Concurrent European Service, which provides a solution in the event that NICE cannot be part of the Parallel EMA EUnetHTA consultation process after the UK leaves the European Union
- Parallel Consultation with the European Medicines Agency (EMA) and European Network for Health Technology Assessment (EUnetHTA)
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Blue Cross/Blue Shield (BCBS) to identify a company for the first scientific advice discussions started with a US payer

Processes and Guidelines - NICE Processes and Guidelines Development

The meeting also discussed evolving processes within the technical engagement step to increase efficiencies and communication, including several key objectives.

- Accelerating the HTA and commercial negotiation processes for faster patient access and less intensive resource use for NICE
- Greater importance placed on the technical engagement step in the HTA process with earlier involvement of committee members to reduce uncertainties in the evidence base and prevent the need for multiple committee meetings
- Accommodating the needs of small companies to make the process easier to understand and navigate

New Technologies - Challenges and Opportunities from New Technologies

There was a particular emphasis on new technologies, including how NICE can lead the evaluation of genomic tools and treatments, along with the fight against antimicrobial resistance.

Insights from the HTAi 2019 Annual Meeting

In June 2019, members of Health Technology Assessment international (HTAi) gathered for their annual meeting to discuss the future of health technology assessment (HTA) as we move into the next decade. The HTAi society represents "an open platform for global collaboration that leverages and shares collective intelligence to improve health outcomes worldwide." Its members hail from a variety of organizations, including HTA bodies, academic institutions, pharmaceutical industry, patient groups, research companies, and consultancies.

This meeting facilitated a collaborative environment for members to present their research and share perspectives on the current status of HTA methodologies and decision making and how these must evolve to meet the challenges of HTA in the next decade. However, with challenge comes opportunity; while digitalization and innovation represent risk of disruption to HTA, there is clear potential to utilize new tools to harmonize and standardize HTA, improve efficiency, and optimize overall value and outcomes for patients and stakeholders.

The theme of this year's meeting was HTA Beyond 2020: Ready for the New Decade? Members explored future priorities and discussed how HTA may change over the next decade, focusing on the following key topics.

Joint HTA: One Size Fits All?

There is a need for increased collaboration to help standardize assessments and reduce duplication, but is this feasible and valuable as a global approach?

The Rise of Digital Health: Innovator or Disruptor?

Increased digitization has the potential to generate big data and improve HTA processes; how do we ensure this adds value and prevents disruption?

Global Collaboration is Required to Optimize the Value of Real-World Evidence (RWE)

Real-world evidence (RWE) has potential to help determine value of technologies for pricing, reimbursement, and market access (PRMA) decision making across the lifecycle of a product. However, significant challenges are associated with RWE generation and can only be overcome with global collaboration.

Patient Involvement in HTA

Patient preferences are increasingly included in HTA assessments, but how should this value be measured for inclusion in HTA methodologies and what is the overall benefit to manufacturers?

Several Evidera staff members attended the HTAi annual meeting and have compiled a highlight of these key topics of focus during the 2019 meeting and our understanding of key takeaways, which both suggest HTA priorities for 2020 and beyond and describe how HTA can be expected to change in the next decade. The complete ebook of these insights can be read on our website: https://www.evidera.com/wp-content/uploads/2019/09/2019_HTAi-Annual-Meeting-ebook_FINAL.pdf

Evidera Presents at ISPOR Europe 2019

2-6 November 2019 – Copenhagen, Denmark

SHORT COURSES

Sat., Nov. 2, 08:00 – 12:00
MORNING SESSION

Introduction to the Design & Analysis of Observational Studies of Treatment Effects Using Retrospective Data Sources

Justo N, Martin B

Sun., Nov. 3, 08:00 – 12:00
MORNING SESSION

Using Multi-Criteria Decision Analysis in Healthcare Decision Making- Approaches & Applications

Devlin N, IJzerman M, **Marsh K**

Sun., Nov. 3, 13:00 – 17:00
AFTERNOON SESSION

Creating Natural, Flexible Models with DICE Simulation

Caro JJ, Moller J

WORKSHOPS

Mon., Nov. 4, 17:00 – 18:00
BREAKOUT SESSION 4

W7: ADVANCED WORKSHOP: Using Patient Preference Data to Support Reimbursement and Pricing Decisions: Current Practice, Opportunities, and Challenges

Mühlbacher AC, **Marsh K**, Ghabri S, Lundin D

Tue., Nov. 5, 14:15 – 15:15
BREAKOUT SESSION 6

W11: ADVANCED WORKSHOP: Looking Beyond Statistical Adjustment to Untangle the Effects of Subsequent Treatments Selected by Investigators in Oncology Trials

Ishak KJ, Abrams KR, Muszbek N

Wed., Nov. 6, 08:30 – 09:30
BREAKOUT SESSION 9

W17: Using Patient Preference Data to Support Clinical Trial Design: Current Practice, Opportunities and Challenges

Marsh K, Morrison D, Oehrlein E, **Heidenreich S**

Wed., Nov. 6, 09:45 – 10:45
BREAKOUT SESSION 10

W20: A Quantitative Benefit-Risk Assessment by Applying the Principles of the European Medicines Agency Benefit Risk Assessment Framework and the Publicly Available, Open Source Tool ADDIS: A Hands-On Workshop

Ataher QS, Postmus D, Hillege HL, **Tervonen T**

ISSUE PANEL

Tue., Nov. 5, 17:00 – 18:00
BREAKOUT SESSION 8

IP15: Reduction of Bias or a Burden? The Use of Individual-Patient Models for Submission to HTA Authorities

Joore M, **Caro JJ**, Tappenden P, Ramaekers B

ISPOR FORUM

Mon., Nov. 4, 12:30 – 13:45

Value Demonstration and HTA of Next Generation Diagnostic Testing Approaches: Current State and Future Needs for Driving Precision Medicine Expansion

Spinner D, Schroader B, Ransom J, Siebert U, **Faulkner E**

POSTERS

Mon., Nov. 4
RESEARCH POSTER SESSION 1

PNS: NO SPECIFIC DISEASE

PNS22: Using Twitter to Harvest Data from Scientific Conferences: A Proof of Concept of a New Approach to Retrieve Clinical Trial Results

Prawitz T, Kapetanakis V, Ishak KJ

PNS26: Using Surrogates for Prediction Overall Survival in Oncology: Considerations for New Treatments and Earlier Stages of Cancer

Sorensen S, Kansal AR, Ishak KJ

PNS32: Automatic Abstract Screening Using Machine Learning Techniques: Are We There Yet and How Can We Move Forward?

Rivolo S, Marczell K, Dillon-Murphy D, Sarri G, Benedict A

PNS202: Parallel Scientific Advice from NICE and CADTH: What's in it for Manufacturers?

Vania DK, Boss J, Molenkamp L, Hurley PT, Iheanacho I, Bending M, Deshpande S

PNS250: CADTH Parallel Scientific Advice Programs with NICE and Health Canada

Boss J, Sood A, Mujoomdar M, **Hurley P, Bending M**

PNS346: Can Meta-Analyses Help in Synthesizing Data Across Health Economic Studies?

Kazmierska P, Akinola T, Abogunrin S

PSY: SYSTEMIC DISORDERS/CONDITIONS

PSY43: Health State Utilities Associated with Sickle Cell Disease and its Treatment: Literature Review

Deger KA, Gallagher M, **Stewart K, Matza LS**

Mon., Nov. 4
RESEARCH POSTER SESSION 2

PCN: CANCER

PCN60: Value of Neoadjuvant IO Therapies with or without Adjuvant Cancer Therapies: A Model Framework

Benedict A, Kovacs V, Gal P, Tichy E

PCN 150: Impact of Using Immature Survival Data on NICE Decision-Making

Tai TA, Latimer NR, **Benedict A, Kiss Z, Nikolaou A**

PCN 173: Accounting for Time-Dependent Health State Membership in Budget Impact Analysis - Case Study in Oncology

AWARD FINALIST

Litkiewicz M, Ambavane A, Tosh J

PCN275: The Global Epidemiology of Peripheral T-Cell Lymphoma: A Systematic Review

Abogunrin S, **Panchmatia H**, Ovcinnikova O, Dalal M, Ashaye AO

PCN319: Contemporary Evidence on Global Economic Burden of Frontline Care for Peripheral T-Cell Lymphoma

Ashaye AO, Abogunrin S, **Panchmatia H**, Ovcinnikova O, Dalal M

PCN426: When Cross-Over Isn't Cross Over. Strategies for Handling Effective Subsequent Therapies in Economic Analysis of Oncology Trials

Chapman R, Kongnakorn T

PCN453: Modeling the Impact of Next Generation Sequencing Based Comprehensive Genomic Profiling Panel on Treatment Practices in Advanced or Metastatic Cancer

Quon P, Peng S, **Kansal A, Ye W, Spinner D, Feng H**, Schroeder B, **Faulkner E**

PCN455: Quality of Life of Patients Living with Metastatic Colorectal Cancer (MCRC): Final Results from a European Patient Survey

Benedict A, Rakonczai P, Muszbek N, Maravic Z

Tue., Nov. 5
RESEARCH POSTER SESSION 3

PDB: DIABETES/ENDOCRINE/METABOLIC DISORDERS

PDB106: Does Mobile Health Live Up to Expectations? Exploring Real-World Experiences in Patients with Diabetes

Booth A, Pan S, Cox A, **Merinopoulou E, Oguz M, Halhol S**

PDB112: Experiences of Patients with Type 2 Diabetes Mellitus Patients in the Kingdom of Saudi Arabia

Strizek AA, **Shalhoub H, Matza LS, Jordan J, Anand SB**, Boye KS, Alhammad A, Ekhzaimy A, **Gelhorn HL**

PIN: INFECTIOUS DISEASES

PIN41: Two-Dose Universal Varicella Vaccination in Brazil: A Model-based Evaluation of Long-Term Health and Cost Impact

Safadi M, Wolfson L, Moreira TNF, Chabrol Haas L, Parellada C, **Sutton K, O'Brien E, Gani R**, Pawaskar M

PIN77: Efficacy Misapplication in Vaccine Modelling

Sutton K, Aponte Ribero V, Roiz J

PIN86: Clinical and Economic Outcomes Associated with Varying Coverage of Varicella Vaccination Strategies in Switzerland

Heininger U, Wolfson L, Lienert F, Kyle J, **Sutton K**, Guggisberg P, **Prawitz T, O'Brien E, Gani R**, Pawaskar M

Tue., Nov. 5
RESEARCH POSTER SESSION 4

PCV: CARDIOVASCULAR DISORDERS

PCV59: Hospital Length of Stay among Venous Thromboembolism Patients Treated with Apixaban and Warfarin in England

Carroll R, **Lambrelli D, Donaldson R**, Ramagopalan S, Alikhan R

PCV63: What's the Cost of Hospitalisations Due to Heart Failure with Preserved Ejection Fraction in the United States?

Shamliyan TA, Nambiar S, **Martin A**

PCV124: Reporting and Quality of Patient Preference Studies: A Systematic Literature Review in the Cardiovascular Domain

Duenas A, Yuan Z, Levitan B, **Tervonen T**

PCV134: Mobile Health Technology Perceptions and User Experience among Atrial Fibrillation Patients: A Social Media Listening Study

Halhol S, Pan S, Cox A, **Merinopoulou E, Oguz M, Booth A**

PDG: DRUGS & GENERICS

PDG6: A Systematic Literature Review and Network Meta-Analysis (NMA) of Crisaborole 2% Ointment for the Treatment of Mild-to-Moderate Atopic Dermatitis (AD)

Fahrbach K, Tarpey J, Bergrath E, Hughes R, Cha A, Gerber R, Cappelleri JC

PMU: MULTIPLE DISEASES

PMU75: Consumer Value of Antidiabetic, Antineoplastic, and Respiratory Drugs

AWARD SEMI-FINALIST

Ganz ML

PMU110: Optimizing Early Access Through Italy's Pharmaceutical Innovation System: Key Success Factors for Attaining Innovative and Conditionally Innovative Status

Sligh S, Kravetz A

PMU123: Do Systematic Reviews Systematically Assess Risk of Bias in Real-World Evidence Studies?

Kazmierska P, Gomez Espinosa E, Deshpande S, Iheanacho I

Wed., Nov. 6
RESEARCH POSTER SESSION 5

PGI: GASTROINTESTINAL DISORDERS

PGI9: Cost-Effectiveness of Tofacitinib Compared with Infliximab, Adalimumab, Golimumab and Vedolizumab for the Treatment of Moderate to Severe Ulcerative Colitis in Germany

Quon P, Sardesai A, Milev S, DiBonaventura M, Cappelleri JC, Kisser A, Modesto I, Dietz L, Dignass A, Bargo D

PIH: INDIVIDUAL'S HEALTH

PIH54: Health Related Quality of Life of Pre-Adolescent Deaf Children with Cochlear Implants: A Conceptual Disease Model

Cooper O

PND: NEUROLOGICAL DISORDERS

PND93: What Good are Digital Technologies in Alzheimer's Disease Research? - A Systematic Literature Review

Vinals L, Akinola T, Sarri G

PRO: RARE & ORPHAN DISEASES

PRO6: Translation and Linguistic Validation of the Hemophilia Quality of Life (Haemo-QoL-A) Questionnaire for Use with Hemophilia Patients

Parks-Vernizzi E, Benjamin A, Herzberg T, **Rentz A**, Light E

PRO69: Epidemiological Model to Support Orphan Designation Decisions: A DICE Simulation Study

Mohseninejad L, Pelligra C, Caro JJ

PRO89: Too Ultra-Rare for Care? Orphan Drug Availability for Respiratory Diseases: A Systematic Review

AWARD FINALIST

Matthews H, Lovelace M, **Freitag A, Iheanacho I**

PRO109: A Comparative Review of NICE and SMC Decision-Making for Ultra-Orphan Medicines

Gibbs K, Schmetz A, Emich H, Gardner K

Upcoming Presentations

CHEST 2019

October 19-23, 2019; New Orleans, LA, USA

POSTER

Dual-Combination Maintenance Inhaler Preferences in Asthma and Chronic Obstructive Pulmonary Disease: A Patient-Centered Benefit-Risk Assessment

Martinez FJ, **Tervonen T**, Gilbert I, Eudicone JM, **Heidenreich S**, Hanania NA

Southeast SAS Users Group 2019

October 20-22, 2019; Williamsburg, VA, USA

PODIUM

Data-Driven Programming Techniques Using SAS Macros to Semi-Automate Generation of Descriptive Tables in Healthcare Research

Mercaldi K

ISOQOL 2019 26th Annual Conference

October 20-23, 2019; San Diego, CA, USA

WORKSHOP

Clinical Outcome Assessment in a Multi-Cultural Context: Measurement Challenges and Solutions

Martin ML, Hudgens S, Regnault A, Eremenco S, McLeod L

ROUNDTABLES

Developing Clinical Outcome Assessments for Regulatory Purposes

Lenderking W

How to Peer Review a Paper

Feeny D, **Revicki D**

ORAL PRESENTATION

Understanding the Patient Experience in Follicular Lymphoma (FL), Relapsed/Refractory FL (R/R FL), and Relapsed/Refractory Diffuse Large B-Cell Lymphoma (R/R DLBCL)

Bell JA, Cherepanov D, **Revicki D, Speck RM, Swett L**, Stumpo K, Rong Y, Gordon LI

SYMPOSIUM

United States Utility Algorithm for the EORTC QLU-C10D and the FACT-8D: Multi-Attribute Utility Measures Based on Cancer-Specific Quality of Life Instruments

Revicki DA, Norman R, Viney R, Pickard AS, Mercieca-Bebber R, Shaw J, Cella D, King MT

AMCP Nexus 2019

October 29-November 1, 2019; National Harbor, MD, USA

POSTERS

Budget Impact of Introducing Avelumab (AVE) as a Treatment (Tx) for Genitourinary (GU) Cancers, Including 1L Tx for Advanced Renal Cell Carcinoma (aRCC) and 2L Tx for Locally Advanced Metastatic Urothelial Cancer (mUC) in the United States (US)

Kongnakorn T, Bhanegaonkar A, Zheng Y, Kim R, Phatak H

Elagolix Reduces Productivity Losses in Uterine Fibroids Patients with Heavy Menstrual Bleeding - Evidence from Pivotal Trials

Al-Hendy A, Wang A, Wang H, Owens C, **Coyne K**

Psychometric Evaluation of the Functional Impact of Migraine Questionnaire within the COMPEL Trial

Lackner D, Lipton R, **Knoble N**, Gandhi P, **Bushnell D**, Niu X, Hema V

Real-World Treatment Patterns and Costs of Oral Antipsychotics for Treatment of Schizophrenia in the United States

Bessonova L, **Martin A**, Doane MJ, O'Sullivan AK, **Cichewicz A, Snook K, Hughes R**, Harvey PD

Use of Prostanoids for the Treatment of Pulmonary Arterial Hypertension in the United States: Results of Analyses of a Large, United States, Commercially Insured Population

Highland KB, Drake W, Nagao M, **Murphy B**, Pruett J, Tsang Y, **Berger A**

ISCoS 2019

November 5-7, 2019; Nice, France

POSTERS

Incidence of UTI and Other Catheter-Related Complications Following Initiation of Intermittent Catheterization: Experience of Two European SCI Centers

Berger A, Inglese GW, Vos-van der Hulst M, Hofstad C, Goldstine J, **MacLachlan S, Ross L**, Weiss J, Kirschner-Hermanns R

Potential for Selection Bias in Designing "Real-World" Comparative Effectiveness Studies of Brands of Intermittent Catheterization: Experience of Two European SCI Centers

Berger A, Inglese GW, Vos-van der Hulst M, Hofstad C, Goldstine J, **Colby C, MacLachlan S, Ross L**, Weiss J, Kirschner-Hermanns R

DIA Real World Evidence Conference

November 14-15, 2019; Cambridge, MA, USA

CHAIR/SPEAKER

New Platforms for Clinical Research Purposes

Hao Y, **Schaumberg D**

CTAD 2019

December 4-7, 2019; San Diego, CA, USA

ORAL PRESENTATION

Conducting Clinical Trial Simulation to Study Heterogeneity of Trial Outcomes in Amyloid-Modifying Drugs

Tafazzoli A, Chavan A, Kansal A

Recent Presentations

European Society of Gynecology Congress

October 16-19, 2019; Austria, Vienna

POSTER

Bremelanotide Provides Meaningful Treatment Benefits for Premenopausal Women with Hypoactive Sexual Desire Disorder

Koochaki PE, **Revicki DA**, Wilson H, **Pokrzywinski R**, Jordan R, Lucas J

Gene Therapy for Rare Disorders Europe

October 15-17, 2019; London, UK

SPEAKERS

Integrated Scientific Advice to Support Optimized Evidence Development and Obtain Timely Patient Access for Gene Therapies

Bending M, Hurley P

ARM Cell & Gene Meeting on the Mesa

October 2-4, 2019; Carlsbad, CA, USA

SPEAKER

Real-World Evidence to Drive Acceptance and Uptake of Cell and Gene Therapy: Lessons and Best Practices Workshop

Faulkner E, Arjunji R, Barlow J, Cook F, Parasuraman B, Rothera M

ERS 2019

September 28-October 2, 2019; Madrid, Spain

POSTERS

Assessment of Inter- and Intra-Rater Reliability of Objective Cough Frequency in Patients with Chronic Cough

Mines D, **Bacci ED, Shaffer S**, Nguyen AM, Smith JA, **Vernon M**

Relationship between Objective Cough Frequency and Health-Related Quality of Life

Birring S, Muccino D, **Bacci E, Vernon M**, Schelfhout J, Nguyen AM

ESMO Congress 2019

September 27-October 1, 2019; Barcelona, Spain

ORAL PRESENTATION

ESMO-MCBS and Health Technology Assessment (HTA): Does Value For Physicians Correspond to Value for Payers?

Ambavane A, Rivolo S, Rakonczai P, Kapetanakis V, Benedict A

SUNA uroLogic Conference 2019

September 20-23, 2019; Lake Buena Vista, FL, USA

POSTERS

Are All Patients Who Initiate Intermittent Catheterization Equal? Lessons Learned from Analyses of Patients with Recent Spinal Cord Injury Initiating Intermittent Catheterization at Two European Centers

Berger A, Inglese GW, Vos- van de Hulst M, Hofstad C, Goldstine J, **Colby C, MacLachlan S, Ross L**, Weiss J, Kirschner-Hermanns R

Incidence of Urinary Tract Infection and Other Catheter-Related Complications Following Initiation of Intermittent Catheterization among Patients with Recent Spinal Cord Injury at Two European Centers

Berger A, Inglese GW, Vos- van de Hulst M, Hofstad C, Goldstine J, **MacLachlan S, Ross L**, Weiss J, Kirschner-Hermanns R

ISPOR 2019 Bogota

September 12-14, 2019; Bogota, Colombia

SHORT COURSES

Applied Modeling

Caro JJ

Evolution of Value-Assessment Tools in LATAM: How Can the Healthcare Industry Prepare to Optimize Evidence Generation and Demonstrate the Value of Innovation?

Alfonso R, **Caro JJ**, Guarin DF, de Bustamante MM

ISSUE PANEL

Value Assessment Frameworks in Latin America - Are We There Yet?

Brabata C, **Caro JJ**, Mejia A, de Castilla MR

WCLC 2019

September 7-10, 2019; Barcelona, Spain

POSTER

Experiences of Patients on 1st Line Care (EP1C): Symptoms and Impacts of EGFR TKI Therapy on Real-World Daily Lives of NSCLC Patients

Elkins I, Bordoni R, Shenolikar R, Ryden A, **Martin M**, Bakker N, Chung H, Feldman J

ICPE 2019

August 24-28, 2019; Philadelphia, PA, USA

POSTERS

A Real-World Evidence Study of Germline BRCA Mutations and Survival in HER2-negative Breast Cancer

Dalvi T, McLaurin K, Briceno J, **Nordstrom B**, Bennett J, Hettle R, **Murphy B, Collins J**, McCutcheon S

Calculating Prevalence of Spontaneous Abortion in Pregnancy Registries: Slippery Slope

Covington D, Veley K, Buus R, Churchill P

Development of an Integrated Research Network to Facilitate Non-Interventional Research

Reisinger S, **Berger A, Chen D**, Chick S, Kallenbach L, Vernon B, **Payne K**

The Occupational Hazards of Measuring Risk Tolerance: Convergent Validity in Preference Elicitation

Sri Bhashyam S, **Marsh K**, Quartel A, Gershman A, Stadler K

Using Different Look Back Periods to Calculate the Charlson Comorbidity Index (CCI) in NVAF Patients Treated with Oral Anticoagulants (OACs)

Graham S, Schultze A, Nordstrom B, Mehmud F, Ramagopalan S

Utilisation of Linaclotide in the UK

Dhalwani N, Schultze A, Donaldson R, Ukah A, Weissman D, Wang J, **Cid-Ruzafa J**

Validity of Claims-Based Algorithms to Identify Acute Kidney Injury, Acute Liver Injury, Severe Complications of Urinary Tract Infections, Breast Cancer, and Bladder Cancer among Patients with Type 2 Diabetes: A Pilot Study

Zhou CK, Dinh J, Danysh HE, Johannes C, Gutierrez L, Schmid R, Arana A, Kaye JA, Pladevall-Vila M, Garcia-Albeniz X, Hall K, Yin R, **Cid Ruzafa J**, Gilsenan A, Beachler DC

Alzheimer's Association International Conference

July 14-18, 2019; Los Angeles, CA, USA

POSTER

Simulated Cognitive Trajectories in Patients with and without History of Stroke Who Are at Risk of Developing Alzheimer's Disease Using AD ACE

Tafazzoli A, Weng J, Kansal A

iHEA 2019

July 13-17, 2019; Basel, Switzerland

SESSION SPEAKER

Considerations for Modelling Obesity – New Approaches and Recommendations for Path Forward

Frew E, Schwander B, Nuijten M, **Caro JJ**

CIPP 18th International Congress on Pediatric Pulmonology

June 27-30, 2019; Tokyo, Japan

POSTER

Burden of Severe Asthma in Children in the English Primary Care Setting

Lenney W, Hattori T, Gokhale M, Evitt L, **Nordstrom B, Collins J, Schultze A**, Van Dyke MK

DIA 2019

June 23-27, 2019; San Diego, CA, USA

POSTER

A Decision Analytic Benefit-Risk Assessment Framework to Support Portfolio Prioritization Decisions

Quartey G, SriBhashyam S, **Marsh K**, Maiya V

SESSION SPEAKER

Best Practices for Quantitative Benefit-Risk Assessments

Tervonen T

WORKSHOP

One Size Does NOT Fit All: Know How to Adapt Your Communication Style to be Effective Communicating Up, Down and Peer-to-Peer

Richards M, **Chen D**

SPEAKER

Turning the Patient Voice into Impactful and Measurable Results

Latif E, Baransky R

XXIV World Congress on Parkinson's Disease and Related Disorders

June 16-19, 2019; Montreal, Canada

POSTER

Development of Equations to Support Simulation of Progression of Motor and Non-Motor Symptoms: Retrospective Analysis of the Parkinson's Progression Markers Initiative (PPMI) Cohort

Weng J, **Chandler C, Folse HJ**, Altincatal A, **Ward A**

HTAi 2019 Annual Meeting

June 15-19, 2019; Cologne, Germany

WORKSHOP

Discretely-Integrated Condition Event (DICE) Simulation for HTA

Caro JJ, Moller J

POSTER

Health Preference Research in Europe: A Review of its Use in Approval, Reimbursement, Pricing Decisions

Marsh K, Muhlbacher AC, van Til J, Juhnke C

ISSUE PANELS

Integrating Patient Experience in Complex Pharmacological Solutions: Are the HTA Bodies Ready?

Sarri G, Upadhyaya S, Bertelsen N, Kalo Z

Is MCDA for HTA Finally Ready for Prime Time?

Baltussen R, Briggs A, **Marsh K**, Pinzon C

EHA 2019

June 13-16, 2019; Amsterdam, Netherlands

POSTER

Patient Reported Experience from Part 2 of the First Time in Human Study of the BCMA Antibody Drug Conjugate Belantamab Mafotodin (GSK2857916) for Advanced Relapsed Refractory Multiple Myeloma (DREAMM-1)

Popat R, Opalinska J, Eliason L, Willson J, Felber G, Ackert J, **Correll J, Martin ML**, Bruno A

McGill University Pharmacoepidemiology Courses Summer Session 2019

May 27-30, 2019; Montreal, Canada

SHORT COURSE

EPIB 654 - Pharmacoeconomics for Health Technology Assessment

Caro JJ

ATS 2019

May 17-22, 2019; Dallas, TX, USA

POSTERS

Disease Status Affects Symptomatic Patients' Preferences for Maintenance Inhaler Therapies: Discrete Choice Experiment

Hanania NA, **Tervonen T**, Hawken N, Gilbert I, **Heidenreich S**, Martinez FJ

Patient and Physician Preferences for Attributes of Biologic Medication for Severe Asthma

Gelhorn H, Balantac Z, Ambrose C, Chung Y, Stone B

Patient-Decision-Making Around Use of Reliever Inhalers in Mild Asthma

Reddel HK, **Correll J**, Foster JM, Karlsson N, **Martin M**, Keen C

Quantifying Symptomatic Patients' Preferences for Maintenance Inhaler Therapies: Discrete Choice Experiment

Martinez FJ, **Tervonen T**, Hawken N, Gilbert I, **Heidenreich S**, Hanania NA

National Lipid Association Scientific Sessions

May 16-19, 2019; Miami, FL, USA

ORAL PRESENTATION

The STatin Adverse Treatment Experience (STATE) Survey: Experience of Patients Reporting Side-Effects of Statin Therapy

Cheeley MK, Jacobson TA, Jones PH, LaForge R, Maki KC, Lopez AG, Xiang P, **Bushnell DM, Martin ML**, Cohen JD

National Kidney Foundation 2019 Spring Clinical Meetings

May 8-12, 2019; Boston, MA, USA

POSTERS

Targeted Literature Review of Patient-Reported Burden of Anemia in Chronic Kidney Disease

Anatchkova M, Arregui M, Brooks A, Michalopoulos S, Shafai G, Bozas A, Farag YMK, Sanon M

Targeted Review of the Epidemiology and Burden of Anemia in Chronic Kidney Disease

Anatchkova M, Brooks A, Earley A, Michalopoulos S, Shafai G, Bozas A, Farag YMK, Sanon M

AAN American Academy of Neurology

May 4-10, 2019; Philadelphia, PA, USA

POSTER

MANAGE-PD: A Clinician-Reported Tool to Identify Patients with Parkinson's Disease Inadequately Controlled on Oral Medications - Results from Vignette-Based Validation

Antonini A, Odin P, Jalundhwala YJ, Schmidt P, **Skalicky AM, Kleinman L**, Zamudio J, Onuk K, Kukreja P, Bao Y, Cubillos F, Fernandez HH

2019 Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists

May 3-6, 2019; Nashville, TN, USA

POSTER

Elagolix Improves Quality of Life Among Uterine Fibroids Patients with Heavy Menstrual Bleeding in Phase 3 Trials

Al-Hendy A, Soliman AM, Wang H, **Coyne K**, Carr BR

2019 CADTH Symposium

April 14-16, 2019; Edmonton, Alberta, Canada

ISSUE PANEL

Should Suboptimal Clinical Evidence be Used to Inform HTA Recommendations?

Marsh K, Desrosiers N, Chambers A, McCabe C

World Orphan Drug Congress USA

April 10-12, 2019; Oxon Hill, MD, USA

SPEAKER

Patient-Focused Rare Disease Clinical Trial Protocols: Patient-Centered Outcomes and Beyond

Vernon M, Marsh K

AMCP 2019 Annual Meeting

March 25-28, 2019; San Diego, CA, USA

POSTERS

Budget Impact Analysis of One-Time Screening for Atrial Fibrillation in the United States

Oguz M, Lanitis T, Leipold R, Wygant G, Friend K, Li X, Hlavacek P, Mattke S, Singer DE

Factors that Impact Health-Related Quality of Life in Patients with Tardive Dyskinesia: Regression Analyses of Data from the Real-World RE-KINECT Study

Caroff SN, Cutler AJ, **Shalhoub H, Lenderking WR, Yeomans K**, Serbin M, Anthony E, Yonan C

Incidence and Cost of Major Cardiovascular Events among Patients with Chronic Coronary Artery Disease or Peripheral Artery Disease Identified in a Large United States Healthcare Database

Berger A, Bhagnani T, **Murphy B, Nordstrom B**, Zhao Q, Ting W, Leeper N, Berger J

Treatment Patterns and Unmet Need in Advanced Hepatocellular Carcinoma: Analysis of US Department of Defense Military Health System Data

Kim R, **Stokes M**, Marshall A, Wisniewski T, Gricar J, Savidge R, **Shah S, Mercaldi K, Schaumberg D**, Evans A, Mackie V

Recent Publications

Coyne KS, Harrington A, **Currie BM**, **Chen J**, Gillard P, Spies JB. Psychometric Validation of the 1-month Recall Uterine Fibroid Symptom and Health-Related Quality of Life Questionnaire (UFS-QOL). *J Patient Rep Outcomes*. 2019 Aug 23;3(1):57. doi: 10.1186/s41687-019-0146-x.

Gelhorn HL, Balantac Z, Ambrose CS, Chung YN, Stone B. Patient and Physician Preferences for Attributes of Biologic Medications for Severe Asthma. *Patient Prefer Adherence*. 2019 Jul 25;13:1253-1268. doi: 10.2147/PPA.S198953. eCollection 2019.

Matza LS, Stewart KD, Phillips G, Delio P, Naismith RT. Development of a Brief Clinician-Reported Outcome Measure of Multiple Sclerosis Signs and Symptoms: The Clinician Rating of Multiple Sclerosis (CRoMS). *Mult Scler Relat Disord*. 2019 Jun 19;35:253-261. doi: 10.1016/j.msard.2019.06.024. [Epub ahead of print

Abogunrin S, Ashaye AO, Cappelleri JC, Clair AG, **Fahrbach K**, Ramaswamy K, Serfass L, Srinivas S, Thomaidou D, Zanotti G. Safety and Effectiveness of Classical and Alternative Sunitinib Dosing Schedules for Metastatic Renal Cell Carcinoma: A Meta-Analysis. *Future Oncol*. 2019 Jun;15(18):2175-2190. doi: 10.2217/fon-2018-0858.

Anatchkova M, Brooks A, Swett L, Hartry A, Duffy RA, Baker RA, Hammer-Helmich L, Sanon Aigbogun M. Agitation in Patients with Dementia: A Systematic Review of Epidemiology and Association with Severity and Course. *Int Psychogeriatr*. 2019 Mar 11:1-14. doi: 10.1017/S1041610218001898. [Epub ahead of print]

Armstrong AW, Edson-Heredia E, Naegeli AN, Burge R, Poon JL, **Anatchkova M**, Sun L, Zhu B, Wyrwich KW. Development of the Psoriasis Symptoms Scale (PSS) in Patients with Moderate-to-Severe Psoriasis: Qualitative and Quantitative Analyses. *J Dermatolog Treat*. 2019 Jun 3:1-27. doi: 10.1080/09546634.2019.1623370. [Epub ahead of print]

Atkins MB, Tarhini A, Rael M, Gupte-Singh K, **O'Brien E**, Ritchings C, Rao S, McDermott DF. Comparative Efficacy of Combination Immunotherapy and Targeted Therapy in the Treatment of BRAF-Mutant Advanced Melanoma: A Matching-Adjusted Indirect Comparison. *Immunotherapy*. 2019 May;11(7):617-629. doi: 10.2217/imt-2018-0208.

Barra M, Remák E, Liu DD, Xie L, Abraham L, Sadosky AB. A Cost-Consequence Analysis of Parecoxib and Opioids vs Opioids Alone for Postoperative Pain: Chinese Perspective. *Clinicoecon Outcomes Res*. 2019 Feb 22;11:169-177. doi: 10.2147/CEOR.S183404. eCollection 2019.

Berger A, Simpson A, Bhagnani T, Leeper NJ, **Murphy B, Nordstrom B**, Ting W, Zhao Q, Berger JS. Incidence and Cost of Major Adverse Cardiovascular Events and Major Adverse Limb Events in Patients with Chronic Coronary Artery Disease or Peripheral Artery Disease. *Am J Cardiol*. 2019 Jun 15;123(12):1893-1899. doi: 10.1016/j.amjcard.2019.03.022.

Boye KS, **Matza LS, Stewart KD, Jordan J**, Biricolti G, Del Santo S, Perez-Nieves M, Federici MO, Gentilella R, Losi S, Norrbacka K. Patient Preferences and Health State Utilities Associated with Dulaglutide and Semaglutide Injection Devices among Patients with Type 2 Diabetes in Italy. *J Med Econ*. 2019 Aug;22(8):806-813. doi: 10.1080/13696998.2019.1609482.

Boye KS, **Stein D, Matza LS, Jordan J, Yu R**, Norrbacka K, Hassan SW, García-Pérez LE. Timing of GLP-1 Receptor Agonist Initiation for Treatment of Type 2 Diabetes in the UK. *Drugs R D*. 2019 Jun;19(2):213-225. doi: 10.1007/s40268-019-0273-0.

Brooks A, Langer J, **Tervonen T**, Hemmingsen MP, Eguchi K, **Bacci ED**. Patient Preferences for GLP-1 Receptor Agonist Treatment of Type 2 Diabetes Mellitus in Japan: A Discrete Choice Experiment. *Diabetes Ther*. 2019 Apr;10(2):735-749. doi: 10.1007/s13300-019-0591-9.

Bushnell DM, McCarrier KP, Bush EN, Abraham L, Jamieson C, McDougall F, Trivedi MH, Thase ME, Carpenter L, Coons SJ; PRO Consortium's Depression Working Group. Symptoms of Major Depressive Disorder Scale: Performance of a Novel Patient-Reported Symptom Measure. *Value Health*. 2019 Aug;22(8):906-915. doi: 10.1016/j.jval.2019.02.010.

Cella D, Wilson H, **Shalhoub H, Revicki DA**, Cappelleri JC, Bushmakin AG, Kudlacz E, Hsu MA. Content Validity and Psychometric Evaluation of Functional Assessment of Chronic Illness Therapy-Fatigue in Patients with Psoriatic Arthritis. *J Patient Rep Outcomes*. 2019 May 20;3(1):30. doi: 10.1186/s41687-019-0115-4.

Chudasama YV, Khunti KK, Zaccardi F, Rowlands AV, Yates T, Gillies CL, Davies MJ, **Dhalwani NN**. Physical Activity, Multimorbidity, and Life Expectancy: A UK Biobank Longitudinal Study. *BMC Med*. 2019 Jun 12;17(1):108. doi: 10.1186/s12916-019-1339-0.

Cid Ruzafa J, Ulrichsen SP, Bennett D, Ehrenstein V. Post-authorisation Safety Study of Pioglitazone Use and Safety Endpoints of Interest in Denmark After Direct Healthcare Professional Communication. *Drugs Real World Outcomes*. 2019 Aug 2. doi: 10.1007/s40801-019-0160-6. [Epub ahead of print]

Cohen AT, **Berger SE, Milenković D**, Hill NR, Lister S. Anticoagulant Selection for Patients with VTE-Evidence from a Systematic Literature Review of Network Meta-Analyses. *Pharmacol Res*. 2019 May;143:166-177. doi: 10.1016/j.phrs.2019.03.017.

Constantine GD, **Revicki DA**, Kagan R, Simon JA, Graham S, Bernick B, Mirkin S. Evaluation of Clinical Meaningfulness of Estrogen Plus Progesterone Oral Capsule (TX-001HR) on Moderate to Severe Vasomotor Symptoms. *Menopause*. 2019 May;26(5):513-519. doi: 10.1097/GME.0000000000001261.

Dana R, Bradley JL, Guerin A, Pivneva I, Stillman IÖ, Evans AM, **Schaumberg DA**. Estimated Prevalence and Incidence of Dry Eye Disease Based on Coding Analysis of a Large, All-Age United States Health Care System. *Am J Ophthalmol*. 2019 Jun;202:47-54. doi: 10.1016/j.ajo.2019.01.026.

Deniz B, **Ambavane A**, Yang S, Altincatal A, Doan J, Rao S, Michaelson MD. Treatment Sequences for Advanced Renal Cell Carcinoma: A Health Economic Assessment. *PLoS One*. 2019 Aug 29;14(8):e0215761. doi: 10.1371/journal.pone.0215761. eCollection 2019.

Facon T, Dimopoulos MA, Meuleman N, Belch A, Mohty M, Chen WM, Kim K, Zamagni E, Rodriguez-Otero P, Renwick W, Rose C, Tempescul A, Boyle E, Manier S, Attal M, Moreau P, Macro M, Leleu X, Lorraine Chretien M, Ludwig H, **Guo S**, Sturniolo M, Tinel A, Silvia. A Simplified Frailty Scale Predicts Outcomes in Transplant-Ineligible Patients with Newly Diagnosed Multiple Myeloma Treated in the FIRST (MM-020) Trial. *Leukemia*. 2019 Aug 19. doi: 10.1038/s41375-019-0539-0. [Epub ahead of print]

Faulkner E, Spinner DS, Ringo M, Carroll M. Are Global Health Systems Ready for Transformative Therapies? *Value Health*. 2019 Jun;22(6):627-641. doi: 10.1016/j.jval.2019.04.1911.

Gelhorn HL, Gries KS, **Speck RM**, Duus EM, Bourne RK, Aggarwal D, Cella D. Comprehensive Validation of the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) Anorexia/Cachexia Subscale (A/CS) in Lung Cancer Patients with Involuntary Weight Loss. *Qual Life Res*. 2019 Jun;28(6):1641-1653. doi: 10.1007/s11136-019-02135-7.

Globe G, Wiklund I, Mattera M, Zhang H, **Revicki DA**. Evaluating Minimal Important Differences and Responder Definitions for the Asthma Symptom Diary in Patients with Moderate to Severe Asthma. *J Patient Rep Outcomes*. 2019 Apr 3;3(1):22. doi: 10.1186/s41687-019-0109-2.

Gomes MB, Rathmann W, Charbonnel B, Khunti K, Kosiborod M, Nicolucci A, Pocock SJ, Shestakova MV, Shimomura I, Tang F, Watada H, Chen H, **Cid-Ruzafa J**, Fenici P, Hammar N, Surmont F, Ji L; DISCOVER investigators. Treatment of Type 2 Diabetes Mellitus Worldwide: Baseline Patient Characteristics in the Global DISCOVER Study. *Diabetes Res Clin Pract*. 2019 May;151:20-32. doi: 10.1016/j.diabres.2019.03.024.

Goodman GJ, Kaufman J, Day D, Weiss R, **Kawata AK**, Garcia JK, Santangelo S, Gallagher CJ. Impact of Smoking and Alcohol Use on Facial Aging in Women: Results of a Large Multinational, Multiracial, Cross-Sectional Survey. *J Clin Aesthet Dermatol*. 2019 Aug; 12(8); 28-39.

Harrington M, **Hareendran A, Skalicky A**, Wilson H, Clark M, Mikl J. Assessing the Impact on Caregivers Caring for Patients with Rare Pediatric Lysosomal Storage Diseases: Development of the Caregiver Impact Questionnaire. *J Patient Rep Outcomes*. 2019 Jul 23;3(1):44. doi: 10.1186/s41687-019-0140-3.

Harris L, **Graham S, MacLachlan S**, Exuzides A, Jacob S. Healthcare Resource Utilization by Patients with Treatment-Refractory Myasthenia Gravis in England. *J Med Econ*. 2019 Jul;22(7):691-697. doi: 10.1080/13696998.2019.1592180.

Horne L, Ashfaq A, **MacLachlan S**, Sinsakul M, Qin L, LoCasale R, Wetmore JB. Epidemiology and Health Outcomes Associated with Hyperkalemia in a Primary Care Setting in England. *BMC Nephrol*. 2019 Mar 6;20(1):85. doi: 10.1186/s12882-019-1250-0.

Hudgens S, Schüler R, Stokes J, Eremenco S, Hunsche E, Leist TP. Development and Validation of the FSIQ-RMS: A New Patient-Reported Questionnaire to Assess Symptoms and Impacts of Fatigue in Relapsing Multiple Sclerosis. *Value Health*. 2019 Apr;22(4):453-466. doi: 10.1016/j.jval.2018.11.007.

Hummel JP, Leipold RJ, Amorosi SL, Bao H, **Deger KA**, Jones PW, **Kansal AR**, Ott LS, Stern S, Stein K, Curtis JP, Akar JG. Outcomes and Costs of Remote Patient Monitoring among Patients with Implanted Cardiac Defibrillators: An Economic Model Based on the PREDICT RM Database. *J Cardiovasc Electrophysiol*. 2019 Jul;30(7):1066-1077. doi: 10.1111/jce.13934.

Kansal A, Reifsnider OS, Proskorovsky I, Zheng Y, Pfarr E, George JT, Kandaswamy P, Ruffolo A. Cost-Effectiveness Analysis of Empagliflozin Treatment in People with Type 2 Diabetes and Established Cardiovascular Disease in the EMPA-REG OUTCOME Trial. *Diabet Med*. 2019 Jul 11. doi: 10.1111/dme.14076. [Epub ahead of print]

Kawata AK, Hareendran A, Shaffer S, Mannix S, Thach A, Desai P, Mikol DD, Ortmeier B, Bayliss M, Buse DC. Evaluating the Psychometric Properties of the Migraine Functional Impact Questionnaire (MFIQ). *Headache*. 2019 Jun 5. doi: 10.1111/head.13569. [Epub ahead of print]

Kawata AK, Lenderking WR, Eseyin OR, Kerstein D, Huang J, Huang H, Zhang P, Lin HM. Converting EORTC QLQ-C30 Scores to Utility Scores in the Brigatinib ALTA Study. *J Med Econ*. 2019 Sep;22(9):924-935. doi: 10.1080/13696998.2019.1624080.

Keyloun KR, Weber DJ, Gardstein BM, **Berger A**, Gillard P, **Ganz ML**. Economic Burden of Hospital Admissions for Patients with Acute Bacterial Skin and Skin Structure Infections in the United States. *Hosp Pract (1995)*. 2018 Dec;46(5):278-286. doi: 10.1080/21548331.2018.1506673.

Khunti K, Chen H, **Cid-Ruzafa J**, Fenici P, Gomes MB, Hammar N, Ji L, Kosiborod M, Pocock S, Shestakova MV, Shimomura I, Tang F, Watada H, Nicolucci A; DISCOVER investigators. Glycaemic Control in Patients with Type 2 Diabetes Initiating Second-Line Therapy: Results from the Global DISCOVER Study Programme. *Diabetes Obes Metab*. 2019 Aug 29. doi: 10.1111/dom.13866. [Epub ahead of print]

King MT, Dueck AC, **Revicki DA.** Can Methods Developed for Interpreting Group-level Patient-reported Outcome Data be Applied to Individual Patient Management? *Med Care*. 2019 May;57 Suppl 5 Suppl 1:S38-S45. doi: 10.1097/MLR.0000000000001111.

Kongnakorn T, Wagenlehner F, Falcone M, **Tichy E**, Di Virgilio R, Baillon-Plot N, Charbonneau C. Cost-Effectiveness Analysis of Ceftazidime/Avibactam Compared to Imipenem as Empirical Treatment for Complicated Urinary Tract Infections. *Int J Antimicrob Agents*. 2019 Jun 13. pii: S0924-8579(19)30161-X. doi: 10.1016/j.ijantimicag.2019.06.008. [Epub]

Krohe M, Tang DH, Klooster B, **Revicki D**, Galipeau N, Cella D. Content Validity of the NFBSI-16 and PROMIS Physical Function Short Form with Advanced Breast Cancer Patients. *Health Qual Life Outcomes*. 2019 May 29;17(1):92. doi: 10.1186/s12955-019-1162-5.

Lanitis T, Proskorovsky I, Ambavane A, Hunger M, Zheng Y, Bharmal M, Phatak H. Survival Analysis in Patients with Metastatic Merkel Cell Carcinoma Treated with Avelumab. *Adv Ther*. 2019 Sep;36(9):2327-2341. doi: 10.1007/s12325-019-01034-0.

Lenderking WR, Lin H, **Speck RM**, Zhu Y, Huang H, Huang J, Kerstein D, Langer CJ. Patient-Reported Outcomes and Quality of Life in Advanced ALK+ Non-Small-Cell Lung Cancer Trial of Brigatinib (ALTA). *Future Oncol*. 2019 Aug;15(24):2841-2855. doi: 10.2217/fon-2019-0185.

Lin H, Agarwal S, **Betts M, Fahrbach K, Chitnis M**, Polydefkis M. Response to the letter to the editor on "An Indirect Treatment Comparison of the Efficacy of Patisiran and Tafamidis for the Treatment of Hereditary Transthyretin-Mediated Amyloidosis with Polyneuropathy". *Expert Opin Pharmacother*. 2019 Aug;20(12):1529.

Lodise T, **Berger A**, Altincatal A, Wang R, Bhagnani T, Gillard P, Bonine NG. Antimicrobial Resistance or Delayed Appropriate Therapy—Does One Influence Outcomes More Than the Other among Patients with Serious Infections Due to CRE vs CSE Enterobacteriaceae? *Open Forum Infect Dis*. 2019 Apr 23;6(6):ofz194. doi: 10.1093/ofid/ofz194.

Lodise TP, Bonine NG, Ye JM, **Folse HJ**, Gillard P. Development of a Bedside Tool to Predict the Probability of Drug-Resistant Pathogens among Hospitalized Adult Patients with Gram-Negative Infections. *BMC Infect Dis*. 2019 Aug 14;19(1):718. doi: 10.1186/s12879-019-4363-y.

Loftus J, Camacho-Hubner C, Hey-Hadavi J, **Goodrich K**. Targeted Literature Review of the Humanistic and Economic Burden of Adult Growth Hormone Deficiency. *Curr Med Res Opin*. 2019 Jun;35(6):963-973. doi: 10.1080/03007995.2018.1546682. Epub 2018 Dec 10.

Luce BR, Simeone JC. How Different is Research Done by the Patient-Centered Outcomes Research Institute, and What Difference Does It Make? *J Comp Eff Res*. 2019 Aug 22. doi: 10.2217/cer-2019-0054. [Epub ahead of print]

Marsh K, Hawken N, **Brookes E**, Kuehn C, Liden B. Patient-Centered Benefit-Risk Analysis of Transcatheter Aortic Valve Replacement. *F1000Res*. 2019 Apr 8;8:394. doi: 10.12688/f1000research.18796.1. eCollection 2019.

Marshall DA, MacDonald KV, **Heidenreich S**, Hartley T, Bernier FP, Gillespie MK, McInnes B, Innes AM, Armour CM, Boycott KM. Correction: The Value of Diagnostic Testing for Parents of Children with Rare Genetic Diseases. *Genet Med*. 2019 Jul 18. doi: 10.1038/s41436-019-0615-x. [Epub ahead of print]

Marshall DA, MacDonald KV, **Heidenreich S**, Hartley T, Bernier FP, Gillespie MK, McInnes B, Innes AM, Armour CM, Boycott KM. The Value of Diagnostic Testing for Parents of Children with Rare Genetic Diseases. *Genet Med*. 2019 Jun 26. doi: 10.1038/s41436-019-0583-1. [Epub ahead of print]

Marshall RD, Collins A, Escolar ML, Jinnah HA, Klopstock T, Kruer MC, Videnovic A, Robichaux-Viehoever A, Burns C, **Swett LL, Revicki DA**, Bender RH, **Lenderking WR**. Diagnostic and Clinical Experience of Patients with Pantothenate Kinase-Associated Neurodegeneration. *Orphanet J Rare Dis*. 2019 Jul 12;14(1):174. doi: 10.1186/s13023-019-1142-1.

Martin AL, Reeves AG, **Berger SE**, Fusco MD, Wygant GD, Savone M, **Snook K, Nejati M, Lanitis T**. Systematic Review of Societal Costs Associated with Stroke, Bleeding and Monitoring in Atrial Fibrillation. *J Comp Eff Res*. 2019 Aug 22. doi: 10.2217/cer-2019-0089. [Epub ahead of print]

Martin ML, Stassek L, Blum SI, Joshi AV, Jones D. Development and Adaptation of Patient-Reported Outcome Measures for Patients Who Experience Itch Associated with Primary Biliary Cholangitis. *J Patient Rep Outcomes*. 2019 Jan 15;3(1):2. doi: 10.1186/s41687-018-0090-1.

Matza LS, Brazier JE, **Stewart KD**, Pinto L, Bender RH, Kircik L, **Jordan J**, Kim KJ, Mutebi A, Viswanathan HN, Menter A. Developing a Preference-Based Utility Scoring Algorithm for the Psoriasis Area Severity Index (PASI). *J Med Econ*. 2019 Sep;22(9):936-944. doi: 10.1080/13696998.2019.1627362.

Matza LS, Deger KA, Howell TA, Koetter K, Yeager AM, Hogge D, Fisher V, Louie AC, Chung KC. Health State Utilities Associated with Treatment Options for Acute Myeloid Leukemia (AML). *J Med Econ*. 2019 Jun;22(6):567-576. doi: 10.1080/13696998.2019.1584108.

Matza LS, Deger KA, Vo P, Maniyar F, Goadsby PJ. Health State Utilities Associated with Attributes of Migraine Preventive Treatments Based on Patient and General Population Preferences. *Qual Life Res*. 2019 Sep;28(9):2359-2372. doi: 10.1007/s11136-019-02163-3.

Matza LS, Kim KJ, Yu H, Belden KA, Chen AF, Kurd M, Lee BY, Webb J. Health State Utilities Associated with Post-Surgical Staphylococcus Aureus Infections. *Eur J Health Econ*. 2019 Aug;20(6):819-827. doi: 10.1007/s10198-019-01036-3.

McDonald L, Simpson A, **Graham S, Schultze A, Nordstrom B**, Durani P, Mehmud F, Ramagopalan SV. Google Searches Do Not Correlate with Melanoma Incidence in Majority English Speaking Countries. *NPJ Digit Med*. 2018 Sep 5;1:44. doi: 10.1038/s41746-018-0050-4. eCollection 2018.

McDonald L, **Stein D**, Carroll R, **Soni M, Schultze A**, Ramagopalan S, Wagstaff J. Extracting Data from a Chemotherapy Prescription Platform for Real-World Oncology Research in the UK: A Pilot Study. *Future Oncol*. 2019 Jul;15(21):2471-2477. doi: 10.2217/fon-2019-0150.

McGirr A, Van Oorschot D, Widenmaier R, **Stokes M, Ganz ML**, Jung H, Varghese L, Curran D. Public Health Impact and Cost-Effectiveness of Non-live Adjuvanted Recombinant Zoster Vaccine in Canadian Adults. *Appl Health Econ Health Policy*. 2019 Jun 28. doi: 10.1007/s40258-019-00491-6. [Epub ahead of print]

McHorney CA, Peterson ED, Ashton V, Laliberté F, Crivera C, Germain G, Sheikh N, Schein J, Lefebvre P. Modeling the Impact of RW Adherence to Once-Daily (QD) vs Twice-Daily (BID) Non-Vitamin K Antagonist Oral Anticoagulants on Stroke and Major Bleeding Events among NVAF Patients. *Curr Med Res Opin*. 2019 Apr;35(4):653-660. doi: 10.1080/03007995.2018.1530205

Merinopoulou E, Pokras S, Pimenta JM, Blini V, Veronesi C, Buda S, Degli Esposti L, **Lambrelli D**. The Cost of Preterm Labor and Preterm Birth for Mothers with Uncomplicated Pregnancies and Their Infants in Italy: Retrospective Cohort Study. *Expert Rev Pharmacoecon Outcomes Res*. 2019 Apr;19(2):231-241. doi: 10.1080/14737167.2018.1476340.

Milev S, DiBonaventura MD, **Quon P**, Goh JW, Bourret J, Peeples-Lamirande K, Soonasra A, Cappelleri JC, Quirk D. An Economic Evaluation of Tofacitinib for the Treatment of Moderately-to-Severely Active Ulcerative Colitis: Modeling the Cost of Treatment Strategies in the United States. *J Med Econ*. 2019 Sep;22(9):859-868. doi: 10.1080/13696998.2019.1609481.

Mirkin S, Graham S, **Revicki DA**, Bender RH, Bernick B, Constantine GD. Relationship between Vasomotor Symptom Improvements and Quality of Life and Sleep Outcomes in Menopausal Women Treated with Oral, Combined 17β-Estradiol/Progesterone. *Menopause*. 2019 Jan 9;26(6):637-642. doi: 10.1097/GME.0000000000001294.

Muszbek N, Proudfoot C, Fournier M, Chen CI, Kuznik A, **Kiss Z, Gal P**, Michaud K. Economic Evaluation of Sarilumab in the Treatment of Adult Patients with Moderately-to-Severely Active RA Who Have an Inadequate Response to Conventional Synthetic Disease-Modifying Antirheumatic Drugs. *Adv Ther*. 2019 Jun;36(6):1337-1357.

Namazy JA, Blais L, Andrews EB, Scheuerle AE, Cabana MD, Thorp JM, Umetsu DT, Veith JH, Sun D, Kaufman DG, **Covington DL**, Mukhopadhyay S, Fogel RB, Lopez-Leon S, Spain CV. Pregnancy Outcomes in the Omalizumab Pregnancy Registry and a Disease-Matched Comparator Cohort. *J Allergy Clin Immunol*. 2019 May 27. pii: S0091-6749(19)30690-6. doi: 10.1016/j.jaci.2019.05.019. [Epub ahead of print]

Nelsen LM, Lee LA, Wu W, Lin X, Murray L, Pascoe SJ, **Leidy NK**. Reliability, Validity and Responsiveness of E-RS:COPD in Patients with Spirometric Asthma-COPD Overlap. *Respir Res*. 2019 May 31;20(1):107. doi: 10.1186/s12931-019-1070-6.

Nicolucci A, Charbonnel B, Gomes MB, Khunti K, Kosiborod M, Shestakova MV, Shimomura I, Watada H, Chen H, **Cid-Razufa J**, Fenici P, Hammar N, Surmont F, Tang F, Pocock S. Treatment Patterns and Associated Factors in 14,668 People with Type 2 Diabetes Initiating a Second-Line Therapy: Results from the Global DISCOVER Study Programme. *Diabetes Obes Metab*. 2019 Jul 12. doi: 10.1111/dom.13830. [Epub ahead of print]

Norman R, Mercieca-Bebber R, Rowen D, Brazier JE, Cella D, Pickard AS, Street DJ, Viney R, **Revicki D**, King MT; European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Group and the MAUCa Consortium. U.K. Utility Weights for the EORTC QLU-C10D. *Health Econ*. 2019 Sep 3. doi: 10.1002/hec.3950. [Epub ahead of print]

Padmanathan P, Biddle L, Carroll R, Derges J, Potokar J, Gunnell D. Suicide and Self-Harm Related Internet Use. *Crisis*. 2018 Nov;39(6):469-478. doi: 10.1027/0227-5910/a000522.

Pang H, Wang M, Kiff C, **Soni M, Stein D**, Tyas D. Early Access to Medicines Scheme: Real-World Data Collection. *Drug Discov Today*. 2019 Jun 19. pii: S1359-6446(19)30083-2. doi: 10.1016/j.drudis.2019.06.009. [Epub ahead of print]

Pinto CA, **Tervonen T, Marsh K, Lambrelli D, Schultze A**, Tershakovec A, Hyacinthe J, **Prawitz T**, Hammad TA. Personalized B-R Assessments Combining Clinical Trial and RW Data Provide Further Insights into Which Patients May Benefit Most from Therapy: Demonstration for a New Oral Antiplatelet Therapy. *Pharmacoepidemiol Drug Saf*. 2019 Apr;28(4):443-451.

Pisetsky DS, Thompson DK, Wajdula J, Diehl A**, Sridharan S**. Variability in Antinuclear Antibody Testing to Assess Patient Eligibility for Clinical Trials of Novel Treatments for Systemic Lupus Erythematosus. *Arthritis Rheumatol*. 2019 Sep;71(9):1534-1538. doi: 10.1002/art.40910.

Pokrzywinski RM, Soliman AM**, Chen J**, Snabes M, Diamond MP, Surrey E, **Coyne KS**. Impact of Elagolix on Work Loss Due to Endometriosis-Associated Pain: Estimates Based on the Results of Two Phase III Clinical Trials. *Fertil Steril*. 2019 Sep;112(3):545-551. doi: 10.1016/j.fertnstert.2019.04.031.

Pokrzywinski RM, Swett LL, Pannaraj PS, Yi J, Pavilack MS, Kumar VR, McLaurin KK. Impact of Respiratory Syncytial Virus-Confirmed Hospitalizations on Caregivers of US Preterm Infants. *Clin Pediatr (Phila)*. 2019 Jul;58(8):837-850. doi: 10.1177/0009922819843639.

Proskorovsky I, Su Y, **Fahrbach K**, Vandendries E, **Pagé V**, Onyekwere U, Wang Y, Cappelleri JC, Stelljes M. Indirect Treatment Comparison of Inotuzumab Ozogamicin Versus Blinatumomab for Relapsed or Refractory Acute Lymphoblastic Leukemia. *Adv Ther*. 2019 Aug;36(8):2147-2160. doi: 10.1007/s12325-019-00991-w. Epub 2019 May 28.

Quon PL, Xiao Y, Sorensen S, Monfared AAT. Economic Evaluation of Nivolumab Plus Ipilimumab Combination as First-Line Treatment for Patients with Advanced Melanoma in Canada. *Pharmacoecon Open*. 2019 Sep;3(3):321-331. doi: 10.1007/s41669-018-0112-1.

Ramagopalan SV, **Graham S**, Carroll R, **Raluy-Callado M, Nordstrom BL, Donaldson R, Colby C**, Mehmud F, Alikhan R. Discontinuation and Primary Care Visits in Nonvalvular Atrial Fibrillation Patients Treated with Apixaban or Warfarin. *J Comp Eff Res*. 2019 Apr;8(6):371-379. doi: 10.2217/cer-2019-0005.

Ramagopalan SV, Malcolm B, **Merinopoulou E**, McDonald L, Cox A. Automated Extraction of Treatment Patterns from Social Media Posts: An Exploratory Analysis in Renal Cell Carcinoma. *Future Oncol*. 2019 Sep 4. doi: 10.2217/fon-2019-0406. [Epub ahead of print]

Ray KK, Kendall DM, Zhao Z, Peng X, Enrique Caballero A, Polonsky WH, **Nordstrom BL**, Fan L, Curtis BH, Davies MJ. A Multinational Observational Study Assessing Insulin Use: Understanding the Determinants Associated with Progression of Therapy. *Diabetes Obes Metab*. 2019 May;21(5):1101-1110. doi: 10.1111/dom.13622.

Reckamp K, Lin HM, Huang J, **Proskorovsky I**, Reichmann W, **Krotneva S**, Kerstein D, Huang H, **Lee J**. Comparative Efficacy of Brigatinib versus Ceritinib and Alectinib in Patients with Crizotinib-Refractory Anaplastic Lymphoma Kinase-Positive Non-Small Cell Lung Cancer. *Curr Med Res Opin*. 2019 Apr;35(4):569-576. doi: 10.1080/03007995.2018.1520696.

Reed SD, Dubois RW, Johnson FR, **Caro JJ**, Phelps CE. Novel Approaches to Value Assessment Beyond the Cost-Effectiveness Framework. *Value Health*. 2019 Jun;22(6S):S18-S23. doi: 10.1016/j.jval.2019.04.1914.

Revicki DA, Speck RM, Lavoie S, Puelles J, Kuo B, Camilleri M, Almansa C, Parkman HP. The ANMS GCSI-DD: Psychometric Evaluation in Patients with Idiopathic or Diabetic Gastroparesis. *Neurogastroenterol Motil*. 2019 Apr;31(4):e13553. doi: 10.1111/nmo.13553.

Sarri G, Guo Y, **Iheanacho I**, Puelles J. Moderately Severe and Severe Acute Pancreatitis : A Systematic Review of the Outcomes in the USA and European Union-5. *BMJ Open Gastroenterol*. 2019 Feb 16;6(1):e000248. doi: 10.1136/bmjgast-2018-000248. eCollection 2019.

Scheuerle AE, Holmes LB, Albano JD, Badalamenti V, Battino D, **Covington D**, Harden C, Miller D, Montouris GD, Pantaleoni C, Thorp J, Tofighy A, Tomson T, Golembesky AK. Levetiracetam Pregnancy Registry: Final Results and a Review of the Impact of Registry Methodology and Definitions on the Prevalence of Major Congenital Malformations. *Birth Defects Res*. 2019 Aug 1;111(13):872-887. doi: 10.1002/bdr2.1526.

Schneider G, Banaschewski T, Feldman BL, Gustafsson PA, **Murphy B**, Reynolds M, Coghill DR, Spalding WM. Weight and Height in Children and Adolescents with ADHD: A Longitudinal Database Study Assessing the Impact of Guanfacine, Stimulants, and No Pharmacotherapy. *J Child Adolesc Psychopharmacol*. 2019 May;29(4):285-304. doi: 10.1089/cap.2018.0132.

Schultze A, Graham S, Nordstrom BL, Mehmud F, Ramagopalan SV. Commonly Used Definitions in Real-World Studies May Underestimate the Prevalence of Renal Disease among Nonvalvular Atrial Fibrillation Patients. *J Comp Eff Res*. 2019 Jul 18. doi: 10.2217/cer-2019-0070. [Epub ahead of print]

Shantakumar S, **Nordstrom BL**, Hall SA, Djousse L, van Herk-Sukel MPP, **Fraeman KH**, Gagnon DR, Chagin K, Nelson JJ. Prescriber Compliance with Liver Monitoring Guidelines for Pazopanib in the Postapproval Setting: Results from a Distributed Research Network. *J Patient Saf*. 2019 Mar;15(1):55-60. doi: 10.1097/PTS.0000000000000332.

Siffel C, **Kistler KD**, Lewis JFM, Sarda SP. Global Incidence of Bronchopulmonary Dysplasia among Extremely Preterm Infants: A Systematic Literature Review. *J Matern Fetal Neonatal Med*. 2019 Aug 9:1-11. doi: 10.1080/14767058.2019.1646240. [Epub ahead of print]

Simeone JC, Nordstrom BL, Patel K, Klein AB. Treatment Patterns and Overall Survival in Metastatic Non-Small-Cell Lung Cancer in a Real-World, US Setting. *Future Oncol*. 2019 Sep 9. doi: 10.2217/fon-2019-0348. [Epub ahead of print]

Simeone JC, Nordstrom BL, Patel K, Mann H, Klein AB, Horne L. Treatment Patterns and Overall Survival in Metastatic Urothelial Carcinoma in a Real-World, US Setting. *Cancer Epidemiol*. 2019 Jun;60:121-127. doi: 10.1016/j.canep.2019.03.013.

Speck RM, Shalhoub H, Ayer DW, Ford JH, Wyrwich KW, Bush EN. Content Validity of the Migraine-Specific Quality of Life Questionnaire Version 2.1 Electronic Patient-Reported Outcome. *J Patient Rep Outcomes*. 2019 Jul 11;3(1):39. doi: 10.1186/s41687-019-0138-x.

Speck RM, Shalhoub H, Wyrwich KW, **Yu R**, Ayer DW, Ford J, Bush EN, Lipton RB. Psychometric Validation of the Role Function Restrictive Domain of the Migraine Specific QoL Questionnaire v2.1 Electronic Patient-Reported Outcome in Patients with Episodic and Chronic Migraine. *Headache*. 2019 May;59(5):756-774. doi: 10.1111/head.13497.

SriBhashyam S, **Marsh K**, Quartel A, Weng HH, Gershman A, Longo N, Thomas J, Zori R. A Benefit-Risk Analysis of Pegvaliase for the Treatment of Phenylketonuria: A Study of Patients' Preferences. *Mol Genet Metab Rep*. 2019 Aug 30;21:100507. doi: 10.1016/j.ymgmr.2019.100507. eCollection 2019 Dec.

Talbot GH, **Kleinman L**, Davies E, Hunsche E, **Revicki D**, Roberts L, Rosenberg D, Nord CE. Clostridium Difficile Infection-Daily Symptoms (CDI-DaySyms™) Questionnaire: Psychometric Characteristics and Responder Thresholds. *Health Qual Life Outcomes*. 2019 May 3;17(1):77. doi: 10.1186/s12955-019-1142-9.

Tap WD, Gelderblom H, Palmerini E, Desai J, Bauer S, Blay JY, Alcindor T, Ganjoo K, Martín-Broto J, Ryan CW, Thomas DM, Peterfy C, Healey JH, van de Sande M, **Gelhorn HL**, Shuster DE, Wang Q, Yver A, Hsu HH, Lin PS, Tong-Starksen S, Stacchiotti S, Wagner AJ. Pexidartinib versus Placebo for Advanced Tenosynovial Giant Cell Tumour (ENLIVEN): A Randomised Phase 3 Trial. *Lancet*. 2019 Aug 10;394(10197):478-487. doi: 10.1016/S0140-6736(19)30764-0.

Tervonen T, Angelis A, Hockley K, Pignatti F, Phillips LD. Quantifying Preferences in Drug Benefit-Risk Decisions. *Clin Pharmacol Ther*. 2019 Mar 31. doi: 10.1002/cpt.1447. [Epub ahead of print]

Tervonen T, Pignatti F, Postmus D. From Individual to Population Preferences: Comparison of Discrete Choice and Dirichlet Models for Treatment Benefit-Risk Tradeoffs. *Med Decis Making*. 2019 Sep 9:272989X19873630. doi: 10.1177/0272989X19873630. [Epub ahead of print]

Wang W, Moroi S, Bakulski K, Mukherjee B, Weisskopf MG, **Schaumberg D**, Sparrow D, Vokonas PS, Hu H, Park SK. Bone Lead Levels and Risk of Incident Primary Open-Angle Glaucoma: The VA Normative Aging Study. *Environ Health Perspect*. 2018 Aug 8;126(8):087002. doi: 10.1289/EHP3442. eCollection 2018 Aug.

Wang Y, **Coyne K**, Sofen H, Santanello N, **Currie B**, Zhang Z, Nograles K. Qualitative Analysis and Reproducibility Assessment of the Scalp Itch Numeric Rating Scale among Patients with Moderate to Severe Plaque Psoriasis of the Scalp. *J Dermatolog Treat*. 2019 Feb 12:1-35. doi: 10.1080/09546634.2019.1577546. [Epub ahead of print

Evidera Acquires Medimix, Expanding Solutions for Real-World Research

On July 1, 2019, Evidera completed the acquisition of Medimix International, a global technology company providing real-world evidence (RWE) insights and information to the pharmaceutical, diagnostic, and medical device industries. This acquisition enables Evidera to offer its customers enhanced technology solutions, real-world data, and access to healthcare providers.

Medimix solutions help clients gain insight into the real-world performance and outcomes associated with new treatments. Medimix scans, extracts and synthesizes big data and evidence-based information using a proprietary cloud-based visualization and analytics interface. To generate insights, Medimix uses one of the largest panels of healthcare providers globally, totaling 2.2 million clinicians, with a focus on hematology and oncology.

"The addition of Medimix will expand our ability to help our clients plan for and generate the evidence needed to optimize the market access and commercial potential of their products," said Karen Kaucic, MD, president of Evidera. "We look forward to leveraging the capabilities and resources of Medimix to develop novel approaches to access and maximize the utility of real-world data."

Medimix's primary solution, LiveTracker™, is a cloud-based platform that provides real-time monitoring of clients' particular therapeutic markets and drugs via key performance indicators and real-world data. It is unique in its ability to provide robust and comparable real-world evidence in more than 60 countries, including information on market structure, drug awareness and level of adoption, patient profiles, and treatment sequencing and outcomes. Evidera will leverage the platform and the data it generates to power more efficient and effective real-world research that addresses burden of illness, resource utilization, safety, patient outcomes, and other endpoints.

"For more than 25 years, Medimix has offered specialized global business insights and marketing services to the pharmaceutical, diagnostic, and medical device industries," said Henry Gazay, CEO of Medimix. "By joining forces with Evidera, we will better support our existing clients with extended resources and geographic footprint. Our ambition is to bridge the gap between real-world data used for research and commercial purposes, and to offer a wide range of new solutions to the pharmaceutical industry."

Medimix has been recognized by Pharma Tech Outlook as a top 10 pharma analytics solution provider and by CIO Review as one of the 20 most promising pharma and life sciences tech solution providers. The company's diversified blue-chip customer base includes eight of the top 10 largest pharmaceutical companies in the world.

Evidera and CSS Collaborate to Develop Joint Real-World and Patient-Centered Research Capabilities in Japan

Evidera has entered into an exclusive collaboration agreement with Clinical Study Support, Inc. (CSS), a subsidiary of Shin Nippon Biomedical Laboratories Ltd. (SNBL), extending both organizations' capabilities to deliver more robust consulting and analytical capabilities and creating a more complete geographic customer solution for clinical, real-world, and patient-centered research. CSS is a clinical research organization based in Nagoya, Japan, that provides post-market, real-world research services, including database studies, questionnaire development, and pharmacoeconomics.

Together, Evidera and CSS will leverage their combined expertise, including Japan-based multilingual experts, to provide research services to global or Japan-based clients undertaking studies that include a Japanese component. Such research services include the design and implementation of real-world studies, epidemiological studies, qualitative and quantitative patient-centered research, clinical outcome assessment development and validation, patient recruitment for prospective studies, health economics modeling, and market access and health technology assessment consulting services. The companies also are committed to the joint development of direct-to-electronic medical record (EMR) and EMR-enabled observational studies in Japan.

"Our collaboration with Evidera allows us to support larger global projects that may benefit from our knowledge and expertise in Japanese-specific settings," said Tatsuya Isomura, MS, PhD, founder and chief executive officer of CSS. "Our clients will gain access to global project management and operational resources that will enable larger and more complex research programs, as well as more robust evidence of product value and safety."

Karen Kaucic, MD, president of Evidera, said, "This collaboration will allow us to provide broader solutions for our clients as they develop evidence to support regulatory submissions and market access in Japan. We are excited to work with our CSS colleagues to tap into real-world insights from the growing Japanese market, which is already the third-largest drug market in the world, to inform and improve drug development and drug coverage decision-making at a global level."

Evidera and CSS plan to establish a joint office in Japan to facilitate collaboration and efficient project delivery. The two organizations also intend to continue to explore opportunities to expand their joint capabilities in data analytics and management, epidemiology, biostatistics, medical writing, and qualitative research.

Evidera's Eric Faulkner Collaborates with ARM and NAMCP on Recent Study Outlining Recommendations to Increase Patient Access to Transformative Therapies in U.S. Managed Care

Evidera congratulates Eric Faulkner, MPH, Vice President, Precision and Transformative Medicine, on his recent collaboration with the Alliance for Regenerative Medicine (ARM) and the National Association of Managed Care Physicians (NAMCP) on a study of medical director and manufacturer perspectives on value demonstration and reimbursement for cell- and gene-based regenerative and advanced therapies.

The study publication, "Roadmap for Navigating Cell and Gene Therapy Value Demonstration and Reimbursement in U.S. Managed Care," was announced in a joint ARM and NAMCP press release on September 24, 2019. The study characterizes step-by-step considerations for achieving appropriate patient access to transformative and potentially curative therapies in the U.S. managed care setting. The findings identify key issues relevant to value demonstration and access to these therapies at a pivotal time for the industry when several products have reached the market, with many more currently in late-stage clinical trials.

As lead author for the publication, Eric Faulkner commented, "The initial wave of cell and gene therapies has launched into an environment that was not built with transformative or curative therapies in mind. It's crucial for payers, providers, patients, and other stakeholders to align on expectations on value demonstration to ensure sustainable access."

The study highlights Evidera's recognition of this critical point in the evolution of cell and gene therapies and commitment to help bring new treatment options to patients. Evidera's scientific teams understand the concerted effort it takes between healthcare authorities, regulators and drug developers to increase patient access to these potentially curative therapies and can navigate this challenging process.

Learnings for drug developers and payers also highlighted in the study include:

- Reducing barriers to coverage will be critical for equitable patient access to cell and gene therapies
- Improving stakeholder alignment on evidence requirements and a value framework for cell and gene therapies is key to support more rapid coverage and access decisions
- Lack of appropriate fit into existing coding and payment systems creates significant risks for provider adoption and patient access
- Cell and gene therapy manufacturers must think comprehensively and not take anything for granted in developing a value demonstration strategy
- It is critical for commercial payers to actively engage in solutions for making truly transformative therapies available to patients in an affordable manner

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Read the full press release for a more detailed overview or download the study results for more information.

Evidera Welcomes New Senior Experts

Mariah Baltezegar, MBA
Executive Director, Head of Peri- and Post-Approval Virtual Trials

Mariah is responsible for the performance, growth, and development of virtual trial approaches and associated, integrated solutions to meet client needs. For 20 years she has worked in various clinical research positions and has 13 years' experience working in various capacities in the complex space of rare disease development, which has helped her develop a unique perspective of the complicated choreography needed to be successful in rare disease development. Mariah completed her Master of Business Administration degree at the University of North Carolina, Wilmington, and her bachelor's degree in psychology with a minor in statistics from Winona State University.

Ylana Chalem, MSc
Executive Director, RWE Integrated Solutions

Ylana provides scientific leadership to multidisciplinary teams on integrated client solutions, with a focus on linking various study designs and data sources to support integrated evidence plans while promoting sound methodological expertise and ensuring high quality deliverables. She has over 20 years of industry experience and understands how real-world data can help prioritize and streamline decision making and accelerate evidence generation at all stages of drug development. Ylana has a BS in economics and an MS in mathematical economics and econometrics from the Université Pantheon Sorbonne, Paris, and an MS in statistics and computer science from ENSAE (Ecole Nationale de la Statistique et de l'Administration Economique), Paris.

Austin Combest, PharmD, BCOP, MBA
Senior Director, Information and Clinical Science Market Access Consulting

Austin is board certified in oncology and a licensed clinical pharmacist with experience in all phases of drug development from preclinical to Phase IV. He is responsible for coordinating clinical scientist support across all therapeutic areas and providing in-depth support in his expertise area of oncology, including medical consultation, clinical strategy in pre-IND and IND stages, and EMA scientific advice. Austin received specialty post-doctoral training during a two-year oncology drug development and clinical research fellowship with UNC Eshelman School of Pharmacy and PPD. He received his Doctor of Pharmacy degree and Master of Business Administration from Shenandoah University, and a Bachelor of Science degree in molecular biology from East Carolina University.

Barbara Hawkins
Executive Director, Real-World Evidence

Barbara leads the development of commercialization strategies and best practices to support peri- and post-approval studies and identify go-to-market differentiation messaging. She engages collaboratively with both interventional and non-interventional subject matter experts to ensure clinical, scientific, research operations, and innovations excellence. Barbara is a seasoned professional with a strategic and collaborative focus to optimize client relationships. She has over 30 years of experience in the pharmaceutical industry and studied animal science at Rutgers University.

Patricia Hurley, PhD
Senior Director, Strategic Regulatory Consulting
Market Access Consulting

Patricia provides product development and global strategic regulatory advice to external and internal clients, determining the most appropriate strategy for their projects. She works in concert with HTA strategists at Evidera to provide integrated scientific advice to clients to help them align and optimize their evidence generation needs for both approval and access. She has successfully supported many clients with global clinical trial authorization applications and strategic consulting discussions in several disease areas. Patricia has a doctorate in molecular pharmacology and a bachelor's in pharmacology and molecular genetics from University College in Dublin, Ireland.

Erem Latif, MSc, MBA
Director, Patient Engagement
Patient-Centered Research

Erem is an expert in patient-engagement strategy with over 18 years of distinguished implementation of strategic initiatives addressing multiple stakeholder needs across three diverse sectors: clinical research, pharmaceutical/medical devices, and payer pharmacy benefit management. Over the past eight years, Erem has supported the commercial development, launch, and implementation of innovative pilots to improve patient engagement and clinical adherence, leveraging patient-centric strategies, targeted data sets, and integrative healthcare tactics. She received an MBA in healthcare management from the Florida Institute of Technology, an MS in human physiology from Georgetown University, and dual undergraduate degrees from Emory University, with a bachelor's degree in business administration in marketing and business communications, and a Bachelor of Science degree in biology.

Kusuma Mallikaarjun, PhD
Senior Director, Clinical Regulatory Consulting
Market Access Consulting

Kusuma is responsible for developing global regulatory strategies for clients and ensuring effective communication with global health authorities and client leadership teams. She also provides tactical operational support for client programs at various stages of development. Kusuma has over 29 years of extensive regulatory strategy and pharmaceutical development experience across a broad range of therapeutic areas, both directly as a reviewer at the US FDA and in the US pharmaceutical industry, from pre-IND through approval and lifecycle management phases of development. She has a PhD in pharmacokinetics from Virginia Commonwealth University and a bachelor's degree in pharmacy from Bangalore University, India.

Mary Kay Margolis, MPH, MHA
Senior Director, Patient-Centered Clinical Operations, Peri- and Post-Approval Services and Patient-Centered Research

Mary Kay draws from her almost 30 years of experience in clinical research and patient-focused research to bridge the gap between science and clinical operations. She is a strong leader and strategist focused on collaborating with multiple stakeholders on patient-centered initiatives. She previously spent 15 years with Evidera legacy companies and most recently worked at the Patient Centered Outcomes Research Institute (PCORI). Mary Kay has an MPH and an MHA from the University of Pittsburgh Graduate School of Public Health.

John McNamara
Principal Consultant US Commercial Access
Market Access Consulting

John has over 30 years of experience in pricing, reimbursement, and market access of healthcare products and works with clients to help them prepare for commercialization in the US marketplace. He has gained extensive experience in the biopharmaceutical industry through senior positions in both industry and consulting organizations and applies this experience to support clients in planning effective evidence generation strategies to optimize market access of their products. John has been heavily involved in product launches in a variety of therapeutic areas, including specialty, ultra orphan drugs, small molecules, and oncology. He has a Bachelor of Arts degree from the University of Massachusetts, Amherst.

Ann Menzie, MS
Senior Director, Evidence Synthesis,
Modeling & Communication

Ann leads client engagements with a focus on supporting differentiating value propositions using clinical and economic evidence and communicating the value story to key stakeholders in an impactful way. She has held previous industry positions at DePuy Synthes, a Johnson & Johnson company; Vertex Pharmaceuticals; Zimmer; Biomet; and, Mirus Bio (now part of Roche). Ann draws on her deep experience to provide clients with solutions that best fit their needs based on product lifecycle stage and overall market access strategy to communicate value to the right stakeholder at the right time. She has an MS in genetics from the University of Wisconsin-Madison, a master's certificate in health economics and outcomes research from Thomas Jefferson University, and a BS in microbiology from Indiana University-Bloomington.

David Nagel, MEd, MBA
Executive Director, Consulting
Market Access Consulting

David leads Protocol and Trial Optimization (POTO), serving clients as oversight director and project manager, while continuously identifying better ways to meet client needs. David has experience in executive commercial strategy focused on partnerships, rare disease opportunities, and strategic client solutions. He spent 13 years working for GlaxoSmithKline in positions within commercial analysis, strategy, and portfolio management across several different therapeutic areas. David holds a bachelor's degree in mathematics/statistics from Pennsylvania State University, an MEd from Vanderbilt University, and an MBA from Duke University.

Ling Shi, PhD
Director, Clinical Outcome Assessment Analytics and
Senior Research Scientist, Evidence Synthesis,
Modeling & Communication

Ling has extensive experience in clinical trial design and statistical analysis and is proficient with advanced and complex statistical methods such as mixed effects models, survival analysis including competing risk analysis, and nonlinear regression models. She has served as the principal investigator for multiple government-funded and industry-sponsored projects, including large observational studies/registries, and clinical trials. She received her master's degree in biostatistics and PhD degree in child health from Johns Hopkins Bloomberg School of Public Health and her Bachelor of Medicine and master's in medical sciences from Beijing Medical University.

Bill Susanj, MBA
Executive Director, US Practice Lead
Market Access Consulting

Bill provides direction in developing integrated market access and evidence strategies for clients, applying subject area expertise to ensure the highest quality in client deliverables. He has over 25 years' experience in strategic planning, business insights, commercial operations, and advanced analytics that drive business growth in the pharmaceutical industry. He has proven successful at leading the utilization of data, analysis, technologies, strategies, and teams to reveal unprecedented insight into the evolving market access healthcare market. Bill has a Bachelor of Arts degree from the IUP University and a master's from the Joseph M. Katz Graduate School of Business, University of Pittsburgh.

Angela Younger, MS, MBA
Executive Director, Integrated Services
Market Access Consulting

Angela is responsible for the development of unique end-to-end integrated evidence solutions for clients. Having held positions in industry, she has considerable experience within the pharmaceutical and biotech industry leading strategic product development teams to major milestones, including global regulatory interactions, from preclinical stages through life-cycle management. Ms. Younger earned a BS from North Carolina Agricultural & Technical State University, an MS in bio/chemical engineering from The Ohio State University, and an MBA from Saint Joseph's University.

Rebecca Zaha, MPH
Senior Director for Real-World Evidence, China

Rebecca is responsible for developing the strategy to successfully execute RWE research in China, including the methodological and scientific expertise and tailored offerings for the China market. In her role she provides pharmaceutical companies, industry stakeholders, and academia with a knowledge base from which to understand how Chinese RWE can be used across an extensive portfolio of commercial and research needs. She holds a Master of Public Health in epidemiology/biostatistics and international health from Boston University and a Bachelor of Science in Chinese language and literature from Bates College. She also completed courses in Chinese economics, culture, and advanced spoken and written Mandarin at the School for International Training, Kunming in China.

For more detailed information on these experts and other Evidera experts, please visit www.evidera.com/who-we-are/experts/.

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The Evidence Forum is an official publication of Evidera, addressing the scientific and strategic challenges of today's healthcare environment and providing a forum for the exchange of thoughts and ideas focused on evidence and value.

CORPORATE HEADQUARTERS
7101 Wisconsin Avenue, Suite 1400
Bethesda, MD 20814

contact: Susan Potter Couch
phone: +1 301 654 9729
email: info@evidera.com

evidera.com

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