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A Discourse on Value™

MAY 2017

FOCUS ON

Clinical Evidence Planning

Approval to Access

Evidera
Evidence, Value & Access by PPD

MAY 2017

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Evidera
Evidence, Value & Access by PPD

Letter from the President

Jon Williams
President, Evidera

Jon Williams

I am pleased to introduce this spring issue of *The Evidence Forum* and to share some of the excitement we're experiencing as Evidera and PPD continue to work together on behalf of our clients.

Last fall I shared my enthusiasm about joining PPD and spoke of the common goals our organizations have — providing high quality and high impact research, advancing thought leadership and innovation in the industry, and improving patient outcomes. Since then, PPD and Evidera experts have been collaborating on research and providing more efficient and integrated solutions with greater impact.

As a part of PPD, we are now able to help our clients align evidence needs for both regulators and payers for earlier and more efficient trial designs and integrated approaches to real-world evidence development; we can now provide better decision making tools, such as patient preference and benefit-risk assessment across the entire product lifecycle; and, we are developing stronger value propositions and evidence strategies for rare and orphan disease treatments and other emerging and transformative technologies.

In this issue of *The Evidence Forum*, you will see articles written by experts from Evidera and PPD that address some of the areas mentioned above, as well as other topics related to clinical evidence planning for both regulatory approval and market access. As I believe this issue reflects, the demand for stronger evidence to satisfy both regulators and payers is increasing substantially, and our goal is to help our clients provide the real-world evidence needed to bridge this gap between efficacy, safety, and value. We believe this will help ensure patients have access to safe and effective treatments, and, in turn, result in better outcomes and healthier patients.

I hope you find the content in this issue insightful, educational, and useful. As always, we value input and feedback from our readers and welcome your thoughts on the information and services we provide. ■

As President, Jon oversees Evidera's global team of scientists, consultants, and software programmers, providing strategic direction for the company in this rapidly changing healthcare environment. Jon joined UBC in 2010 and oversaw the building of Evidera as an independent company in 2013. He was previously Senior Vice President of Strategy and Business Development at Medco-UBC, where he was responsible for business strategy, organic business development, and establishing partnerships with life sciences and other healthcare organizations. Prior to joining Medco-UBC, Jon was a Senior Principal in the Los Angeles office of the Boston Consulting Group. He has more than 15 years of consulting experience in the healthcare industry, where he has worked extensively with pharmaceutical, biotech, and medical device companies. Jon holds an MBA from the UCLA Anderson School of Management and an undergraduate degree in molecular biology from Brigham Young University.

Clinical Evidence Planning
Approval to Access

Frances C. Macdonald, PhD
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Frances Macdonald

There are few leaders within pharmaceutical companies who would not agree that clinical development must now take into account the needs of health technology assessment (HTA) bodies and payers in addition to the needs of regulatory authorities, such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA). How early these evaluations take place is still a matter of judgment, balancing the costs of researching such needs early, when the risk of clinical failure is high, versus too late, when development plans are largely fixed. In addition, the HTA/payer environment is not static, therefore early assessments need validation as launch approaches. It is clear, however, that commercial success requires strategic regulatory planning plus robust and timely market access planning, and meeting HTA and payer evidence needs is a core part of this package.

While regulators assess the benefit/risk of a new medicine and whether or not the primary endpoint crosses a threshold of 'clinical relevance,' payers have the material, added challenge of valuing the benefit and risk over both the short- and long-term. The increasing flexibility of regulatory authorities in accepting reduced evidence packages in areas of high need is making this a growing challenge.

If we 'stand in the shoes' of those for whom the evidence is being developed, what are their key challenges and concerns? Rising healthcare expenditure is clearly a major concern with, for example, U.S. federal spending estimates for 2017 sitting at $3.65 trillion, up 3.4% from 2016.[1] While drug costs are a relatively small proportion of the total, they are highly visible and thus often the focus of attention. Several reactions have been triggered by concerns over affordability, including a shift of interest from cost to 'value,' albeit that value is multi-faceted with no single definition. HTA agencies assess value using a range of methodologies, including cost-effectiveness and comparative effectiveness. However, as seen with the launch of new, highly effective and generally cost-effective treatments for hepatitis-C, even when cost-effectiveness is demonstrated, if the budget impact of treating all eligible patients is significant,[2] healthcare systems may add further 'value' hurdles. The English HTA body, the National Institute for Health and Care Excellence (NICE), has just announced that drugs assessed as cost effective, but with a projected budget impact of more than £20 million in any of the first three financial years of their use in the National Health Service (NHS), will be the subject of negotiations for commercial agreements to manage costs. Budgets are limited and payers and HTA bodies are clearly under pressure. Systematic and early planning to address these concerns is essential.

As a parallel development, and in part acknowledging the growing complexity of drug development, the FDA and EMA have demonstrated flexibility in supporting innovative trial designs, alternative development pathways, and 'accelerated' access options where clinical need is high. As examples, in 2016 the FDA instituted its Accelerated Approval Program to allow earlier approval of drugs that treat serious conditions and fill unmet medical needs, based on the use of surrogate endpoints. However, from the payers' perspective, these surrogate endpoints need to be validated with regard to quantifying their link with an accepted clinical measure of morbidity or mortality. Also in 2016, the EMA, as part of its stated commitment to enabling early access to medicines which target unmet need or are of a major public health interest,[4] launched a new scheme, PRIME, to further enhance support for the development of such medicines. PRIME, in addition to the options for conditional marketing authorization and compassionate use, are all pathways which raise the possibility of regulatory approval on the basis of a reduced evidence package – raising immediate concerns for payers and HTA bodies who have generally not moved in parallel with regulators and have evaluation methods that rely heavily on receiving data from more conventional development programs. Any company benefiting from these regulatory options to gain early approval clearly needs to have plans in place to fill the evidence

gaps required for national payer and HTA decision makers. It's worthy of note that this additional evidence is also likely to be of high interest to clinician decision makers who may need help to gain confidence in a new medicine approved via an accelerated pathway.

Another area receiving more focus is the impact on, and of, patients in the development and access decisions for new treatments, resulting in more emphasis on the development and use of patient-reported outcomes (PROs). PROs are often used for regulatory purposes, e.g., for either specific label claims or general inclusion within the product summary. In addition, PROs may be used within HTA or payer submissions, sometimes in the form of patient preferences or utilities and as an input to a cost-effectiveness calculation. In many countries these are an expected element, especially if the new medicine is a symptomatic rather than curative treatment. However, PROs required for payers and HTA bodies, which generally need to be described as utilities, may not be the same instruments preferred by regulators, who may, for example, prefer a more sensitive disease-specific instrument. There may also be specific needs associated with special populations, such as paediatrics or rare diseases. Rather than overburden a clinical trial, some of this additional information can potentially be collected from alternative sources, such as existing literature or a PRO-specific prospective study, in parallel with the development program, but again, early planning is essential.

So what solutions exist to successfully navigate this environment and minimize the risk of limited market access? Within Europe, since 2010, the EMA has been supporting the provision of parallel scientific advice from both the EMA and national HTA bodies, providing an excellent opportunity for companies to gain an early understanding of their different perspectives and plan accordingly, noting, of course, that the different national HTA/payer bodies may themselves have different needs. In many cases, as the EMA pilot demonstrated, if planned carefully, one clinical program can meet the core needs of the payers and HTA bodies in addition to the regulators. However, there may be gaps in the payer/HTA package that need to be identified early, with the required evidence developed in parallel with the regulatory programs in order not to delay a successful launch. The relatively new discipline of real-world evidence is increasingly demonstrating its value, not only in filling evidence gaps for HTA and payer discussions, but also in supporting the development of commercial strategy by disclosing the way patients are currently being treated outside clinical trials.

The articles within this edition of *The Evidence Forum* discuss many of the topics above in more detail, demonstrating that to ensure any new medicine reaches patients in a timely manner requires early strategic planning on both regulatory and HTA/payer evidence needs to clearly identify where those evidence needs overlap and to fill gaps as early as possible. While regulators are developing new options to support earlier access for innovative medicines addressing unmet need, payers are under increasing pressure to manage their budgets, and with current funding mechanisms, cannot meet all the needs. Pharmaceutical companies, therefore, need to invest in identifying and addressing their concerns from day one of any development program to plan effectively for evidence generation to support approval and access. ■

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Optimizing Trial Design
Incorporating MCDA into Trial Simulation

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Introduction

Efforts by regulatory agencies to balance the need to ensure rapid access to new drugs with the need to gather data on efficacy and safety have produced a number of innovations in regulatory science.[1] This paper is concerned with two such innovations - the use of modeling and simulation and the use of patient-preference data. Our objective is to consider how they are currently supporting regulators, and how they can be used in combination to improve the efficiency of clinical development, identify differences in benefit-risk balance, and support proactive risk management.

Trial Simulation

Modeling and Simulation (M&S) is being used more and more to understand the likely impact of trial design scenarios on the outcome of an intervention, not only with the objective of preventing failures, but also to increase the probability of success.[2] M&S is used to predict variations in treatment response with factors such as dose, time on treatment, different physiological and pathological conditions, and covariates such as disease severity, co-medication, co-morbidities, and compliance. This insight can be used to perform *in silico* clinical trials, also known as clinical trial simulations (CTS), which enable optimization of the design of prospective trials, including decisions such as the dose, comparator, population, inclusion/exclusion criteria, sample size, and endpoints. By doing so, attrition can be reduced and consequently development costs are lowered. Most importantly, these technologies allow for a kill-fast approach, enabling tough decisions to be made in a timely manner.

The past decade has seen an increase in the appreciation by regulators of the role of M&S in drug development, and an increased influence of M&S on risk/benefit assessment and labeling decisions.[3,4] This interest initially focused on using pharmacokinetic (PK) and pharmacokinetic-pharmacodynamic (PKPD) models to understand dose-response relationships. These principles were already embedded by the U.S. Food and Drug Administration (FDA) in the publication *Guidance for Industry: Population Pharmacokinetics*[5] in 1999 and *Guidance for Industry: Exposure-Response Relationship – Study Design, Data Analysis, and Regulatory Applications* in 2003.[6] This was later complemented by additional guidance, as the applications and demand for M&S increased.

- In 2009, the FDA published its *Guidance for Industry: End-of-Phase 2A Meetings,*[7] encouraging sponsors to seek regulatory meetings at the end of Phase 2A to discuss trial simulation.
- Regulators' collated examples of the impact of M&S on approval. The FDA has published a number of reviews regarding how M&S enabled approval of unstudied dose regimens, provided confirmatory evidence of effectiveness, and utilized primary endpoints derived from model-based approaches.[8] Similar efforts have been undertaken by the European Medicines Agency (EMA), which has organized two major workshops on the subject since 2011.[9]
- Modeling and simulation approaches are included in the FDA's published strategic priorities and are expected to be incorporated in the 2017 Prescription Drug User Fee Act (PDUFA) reauthorisation.[10]

In parallel with these developments, industry has been systematizing its approach to using M&S for drug development. For instance, in 2007 Pfizer published its approach to model-based drug development (MBDD), outlining how decision points throughout the development of their drugs are informed by MBDD, and how PKPD and disease models could be combined with trial performance metrics and decision criteria to support decision making and prioritize compounds. The same approach was used to gather quantitative insight into competitors.[11] Further, industry has evaluated the costs and benefits of using M&S in product development: Pfizer estimated that it enabled a reduction in the annual clinical trial budget of $100 million and increased late-stage clinical study success rates; and Merck & Co./MSD has reported cost savings of $0.5 billion through impact of MBDD on decision-making.[2]

Case Study

An example of the concept has recently been published by Bellanti and collaborators.[12] Clinical trial simulation was used to characterize the time course of five clinical endpoints relevant for the evaluation of iron chelation therapy in pediatric patients affected by chronic iron overload. Partial values and weights for these endpoints were obtained from experts and aggregated into an overall benefit-risk score. The analysis identified alternative regimens that would benefit sub-groups of patients, which was linked back to their different pharmacokinetics and pharmacodynamics. The study demonstrates the feasibility of integrating PKPD relationships into benefit-risk methodologies such as multi-criteria decision analysis (MCDA).

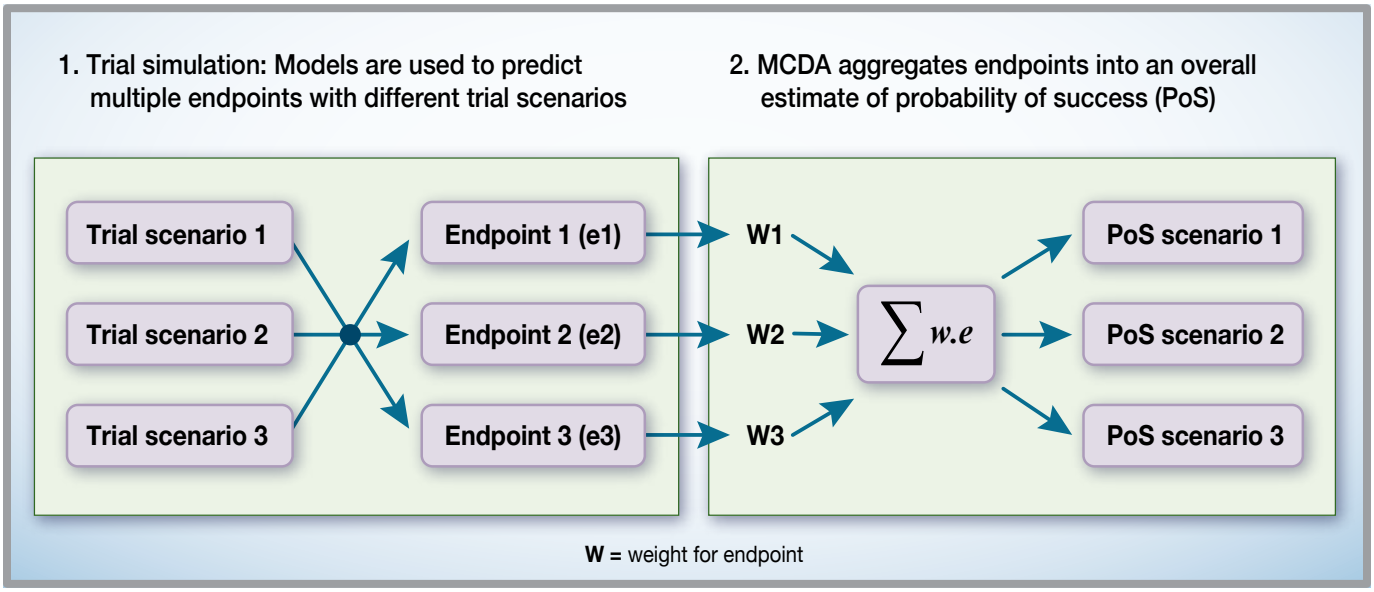
Multi-Criteria Decision Analysis

Multi-Criteria Decision Analysis (MCDA) refers to a collection of analytical methods for supporting decision making and evaluation in the face of multiple, often conflicting, criteria. A number of common steps are often used to define MCDAs, including: defining the decision problem, identifying criteria, measuring the performance of treatments against criteria, eliciting preferences for criteria, and aggregation.[13] The use of MCDA in healthcare has increased over the last 10 years, and it is used to inform many decisions, including: portfolio optimization, approval, reimbursement, and prescription decisions.[13] Given this increased interested in MCDA, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) recently published guidance on good practice in the use of MCDA in healthcare.[14]

In the regulatory space, MCDA is often referred to as quantitative benefit-risk assessment (BRA). The use of MCDA/BRA to support regulatory decision making has been endorsed by a number of authorities, including: the EMA's BRA Methodology project,[15] IMI PROTECT,[16] and ISPOR's working group on risk-benefit management.[17] For instance, the EMA's BRA methodology project concluded that, where the benefit-risk balance was marginal, MCDA could support the approval process.

More recently, both the EMA and the FDA have been investing in projects to determine how to incorporate patients' preferences into regulatory decisions using quantitative BRA. The FDA's Center for Devices and Radiological Health (CDRH) has produced guidance on when and how patient preferences should be elicited to support regulatory decisions.[18] In 2016, CDRH achieved a milestone by approving a weight-loss device, that had failed its primary endpoints, based on work to elicit

Figure 1: Incorporating MCDA into Trial Simulation



patients' preferences, which suggested that patients would accept the mortality risks associated with the device in exchange for the weight loss it generated.[19] Staff at the EMA have also been piloting methods for the elicitation of preferences from patients.[20]

Using MCDA to Support Trial Simulation

While the last decade has seen increased attention of regulators to both MCDA and trial simulation, they have to date been considered separately. There is, however, potential for them to be applied in combination, further enhancing the efficiency of drug development. This is acknowledged in a recent paper authored by two FDA employees, which states:

> *In the near future, CDER plans to issue a series of guidances to enable patient groups, and others, to collect and provide structured input on patient preferences in determining benefit-risk trade-offs, the burden of disease, and patient assessment of present treatments. This input will be used to inform subsequent CDER guidances on ensuring that the structure and assessment of clinical trials are meaningful to patients …*[21]

Specifically, MCDA can support trial simulation by providing a means to reliably estimate the 'probability of success' associated with different trial designs in a manner that reflects stakeholders' preferences. Most importantly, it enhances the value of clinical trial simulations, as it creates the basis for virtual patients, in that both desirable and undesirable effects can be generated at individual patient-level. A trial simulation will invariably predict responses to treatment using multiple endpoints. Comparison of trial design simulations will, therefore, involve trading off performance on these endpoints *(Figure 1)*.

To date, the notion of 'probability of success' employed by trial simulation models has tended to be defined from a commercial perspective, predicting how sales will vary with changes in endpoint predictions.[22] This perspective is still relevant for manufacturers. The use of MCDA can, however, help incorporate relevant perspectives into trial simulations to better predict the probability of approval and reimbursement success. Moreover, it provides insight into patient acceptance and eventually improves the prediction of uptake and sales.

Without MCDA, those responsible for designing trials will continue to do so without understanding what really

Table 1: Perspectives that Can be Incorporated into Trial Simulation Using MCDA

Perspective	Description
Internal	Elicitation of the preference for trial endpoints from multiple internal stakeholders, and facilitation of discussion about which trial scenario is preferred
Regulatory	Elicitation of patient preferences for trial endpoint, and estimation of the probability of which trial scenario would generate the highest benefit-risk balance
Reimbursement	Elicitation of payer preferences for endpoints, and estimation of the probability that a price will be acceptable with each trial scenario

matters to different stakeholders, whose preferences for changes may be different for each endpoint. MCDA offers a weighting mechanism to account for preferences and provides a stronger basis for the probability of success of multiple trial scenarios, as well as the impact of the uncertainty in all these considerations.

Regardless of the perspective, MCDA can facilitate the judgement of how simulation outcomes relate to the probability of success. Depending on the objective of the analysis, MCDA can facilitate multiple perspectives *(Table 1)*.

Conclusion

Clinical drug development is fraught with attrition; benefit–risk assessment should be an integral part of the decision making process in R&D, as it already is for regulators. Whereas historically BRA has been performed retrospectively, the use of M&S can be combined with MCDA to support the evidence synthesis as well as evidence generation before clinical trials are performed or an application is made for market authorization. It is imperative to understand the implications of multiple stakeholders' preferences before implementing costly clinical protocols. We now have the tools to do so. ■

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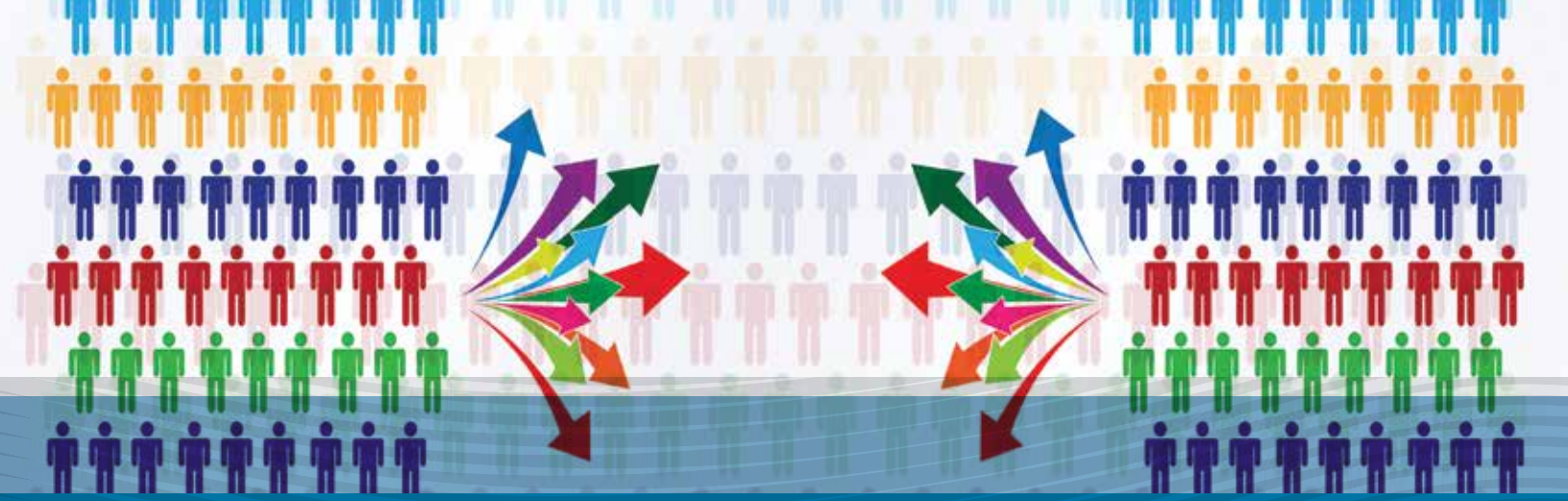

Clinical Trial Simulation
Providing Insight and Interpretation for Alzheimer's Disease Trials

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Introduction

The use of clinical trial simulation (CTS) in new drug development is increasingly being recognized by pharmaceutical companies and regulatory authorities as a cost-effective means to determine which trial designs will be most efficient in detecting therapeutic effect in new drugs.[1] One therapeutic area which may benefit from CTS is Alzheimer's disease (AD), in which the vast majority of clinical trials in recent years have been unsuccessful. An area of particular need is the increased understanding of trials of disease-modifying drugs for AD following several high-profile trial failures over the past year. In this article, we demonstrate the application of CTS in AD trial design using the AD ACE simulator, an analytic framework that places prediction of AD progression and treatment response within the context of a simulated trial design.

An Opportunity to Reassess AD Trial Design with CTS

In the past year, several highly anticipated Phase III trials of disease-modifying drugs in mild to moderate AD, targeting either amyloid or tau pathology, have either failed to meet their primary endpoint or been terminated early. Results from a 15-month trial of the first tau-targeted drug to reach late-stage testing (LMTM) did not show treatment benefits related to cognition and activities of daily living.[2] The EXPEDITION 3 trial found that an amyloid-targeting antibody, solanezumab, failed to meet the primary endpoint of a slowing in cognitive decline.[3] Following this announcement, EXPEDITION PRO, another Phase III study of solanezumab, in which the trial population included only people with prodromal AD, was ended by the sponsor.[4] Similarly, the EPOCH trial of verubecestat, another drug targeting amyloid pathology,

was terminated early based on recommendations from an external Data Monitoring Committee, which saw minimal chance of the trial meeting its primary endpoint.[5]

Despite these recent trial outcomes, there is still substantial support for the amyloid hypothesis, with one proposed explanation for the observed outcomes to be that the involvement of amyloid in AD progression may be more critical in the beginning stages of AD before symptoms occur.[6] According to this hypothesis, amyloid-targeted treatments must be tested in earlier stages of the disease, as is the case in ongoing trials of therapies targeting amyloid pathology in individuals who are healthy but at a genetically high risk of AD.[6] In order to explore this hypothesis, we simulated a trial similar to EXPEDITION 3 while testing several alternate trial designs that probe specific elements of the hypothesis, including sample size, mechanism of action, and population.

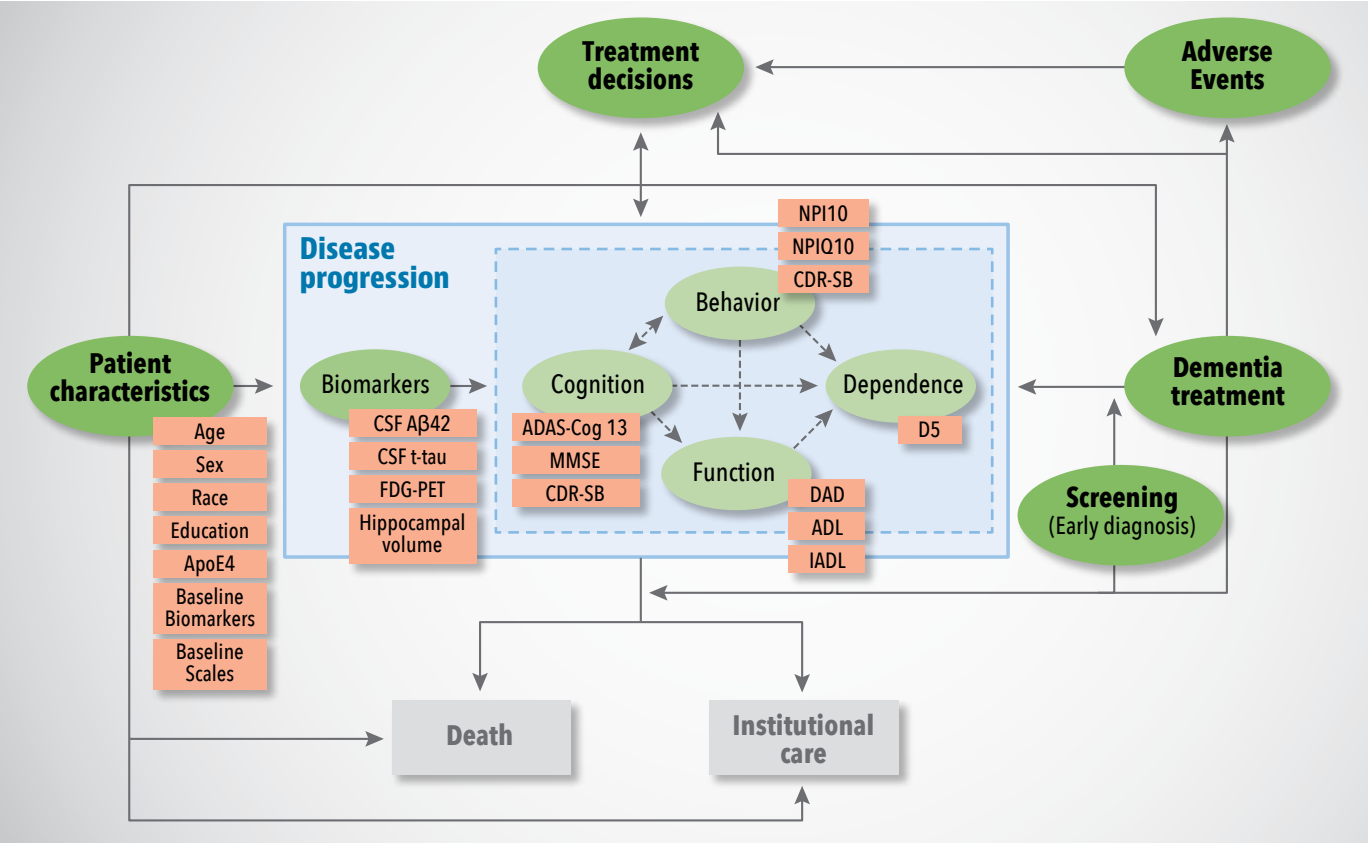
Clinical Trial Simulation with the AD ACE

The AD ACE is a discretely integrated condition event (DICE) simulation of AD developed at Evidera.[7] The simulator incorporates measures of the underlying pathophysiology of AD, including measures of amyloid (CSF Aβ42) and tau (CSF t-tau) levels and their connections to clinical presentation of AD, including cognition and behavioral scales *(Figure 1)*. The relationship between changes in these measures over time are quantified using predictive equations derived from long-term observational data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) to predict natural history of individuals with normal cognition through to severe AD. This design enables the simulation to evaluate the impact of disease-modifying treatments (DMTs) and symptomatic treatments on both the clinical and economic consequences of AD. The AD ACE simulates at the level of individual patient profiles, including explicit quantification of intra- and inter-patient heterogeneity.

"The AD ACE simulates at the level of individual patient profiles, including explicit quantification of intra- and inter-patient heterogeneity."

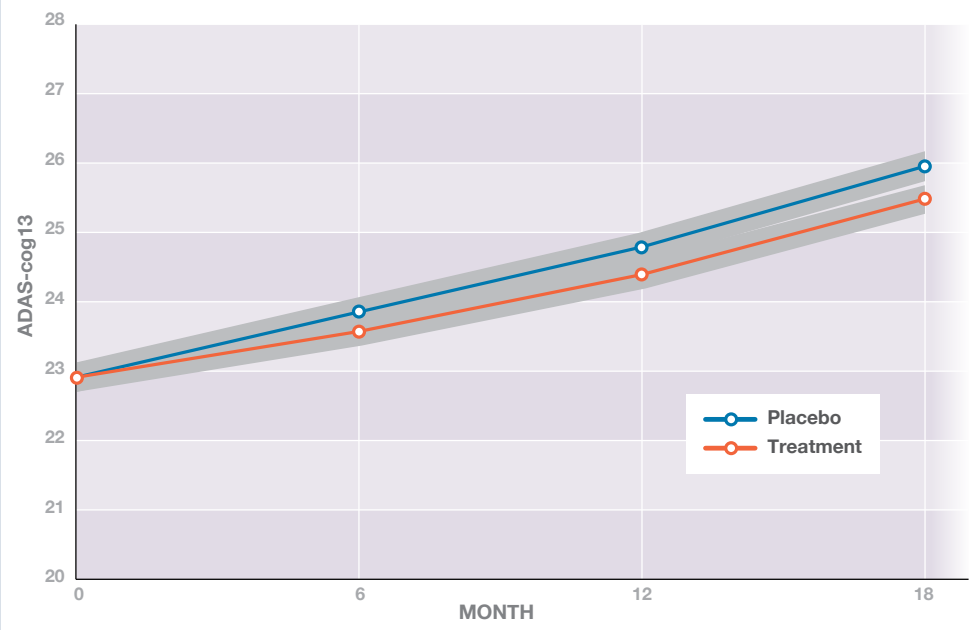
CTS draws from the trajectories for patients with and without treatment predicted by the AD ACE. Patients are included in a simulated trial based on inclusion/exclusion criteria at baseline, and CTS then follows the trajectories

Figure 1. AD ACE Model Diagram



Predictive longitudinal equations that determine trajectories of cognitive decline derived from ADNI and AHEAD (Assessment of Health Economics in Alzheimer's Disease)

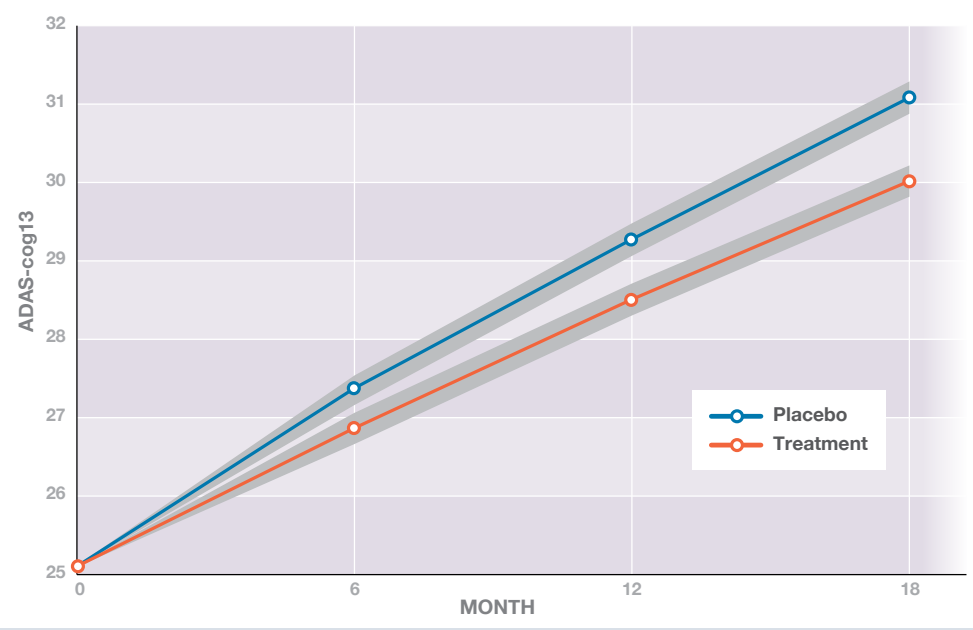
Figure 2. Trajectories of ADAS-Cog from Simulation Based on EXPEDITION 3 Protocol



Trajectories of the median and interquartile range across replications of mean of ADAS-cog score by arm. Simulation of anti-amyloid treatment in a population with mild AD.

of those patients as they proceed through the trial protocol. In order to understand the range of potential trial outcomes, CTS simulates many replications of the specified trial design. For each replication, the endpoints of the trial are assessed using appropriate statistical tests. In this study, we considered Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) change from baseline as the primary endpoint. A successful trial replication was defined to be one in which the primary endpoint showed a difference between the treatment and placebo arms that met statistical significance at the $p < 0.05$ threshold. In order to assess the likelihood of success of a given design, we report the fraction of replications in which the trial was successful. The mean trajectory of ADAS-cog in each arm is also reported for the median replications along with those at the 25th and 75th percentile.

Figure 3. Impact of Greater Therapeutic Effect on Trajectories of ADAS-Cog



Trajectories of the median and interquartile range across replications of mean of ADAS-cog score by arm. Simulation of anti-amyloid and anti-tau treatment in a population with mild AD.

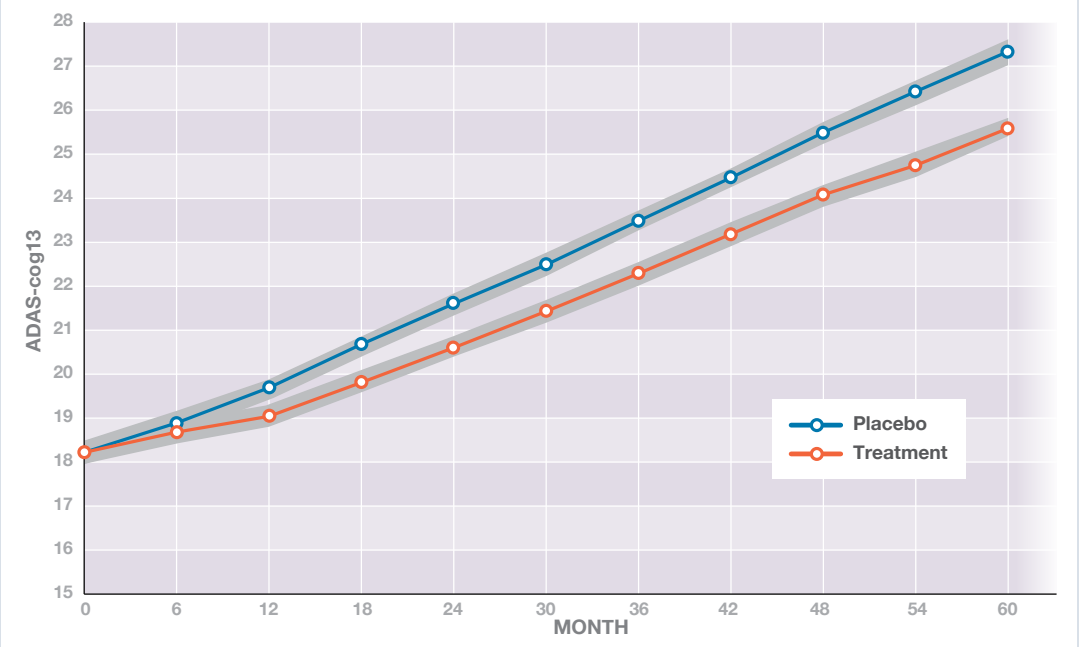
Case Study: CTS Based on EXPEDITION 3 Protocol

In replicating the EXPEDITION 3 protocol, simulated patients were selected according to the eligibility criteria of the trial: patients between the ages of 55 and 90 who were diagnosed with AD and had a Mini-Mental State Examination (MMSE) score of 20 through 26. The trial sample size was 1,000 patients per treatment arm. To mimic the challenges of real clinical data, an annual dropout rate of 10% was applied along with 3% of data missing at random. We assumed complete normalization of amyloid-beta pathology in the simulation, which is likely a substantial overestimate of the true effect of any purely anti-amyloid treatment.[8] The model estimated the likelihood of a successful trial based on the observed difference in ADAS-cog between a treatment which normalized amyloid pathology and placebo at the end of the 18-month trial period. The results suggested a low probability of success (about 10%) for this protocol. We found this was not an issue of sample size, as doubling sample size to 2,000 patients per arm only minimally increased the probability of a statistically significant difference in ADAS-cog to 15% *(Figure 2)*.

Given this low probability of success in the simulations, we sought to explore some of the hypotheses that have been suggested as explanations for the EXPEDITION 3 outcomes. We began by testing whether patients with mild AD might benefit from a larger therapeutic effect on the underlying pathology of AD. To do so, we ran the same CTS of the EXPEDITION 3 protocol with the larger trial population size, while broadening the treatment effect by normalizing both amyloid-beta and tau pathologies. This may reflect either a treatment with a direct effect on both proteins or an interaction between amyloid and tau pathologies beyond that captured in the AD ACE disease model. Under this condition, the simulations yield an increased probability of 84% of observing a statistically significant difference in ADAS-cog after 18 months *(Figure 3)*.

We also evaluate the hypothesis that amyloid-targeting therapies may be effective in asymptomatic stages of AD, exploring a trial population with prodromal AD. Patients were diagnosed with late mild cognitive impairment (LMCI) or early MCI (EMCI) and between the ages of 55 and 90 years. Patients were included only with CSF Aβ42 less than 192 ng/L, which has been shown to correlate with the presence of amyloid plaques in the brain. Again, each treatment arm had 2,000 patients. Treatment had a direct effect only on amyloid pathology. In keeping with the design of ongoing trials in subjects with prodromal AD, we extended the maximum follow-up simulated to five years. Even by two years, however, the probability of showing a statistically significant difference in ADAS-cog was 71% *(Figure 4)*. The improvement in ADAS-cog increased as follow-up continued up to five years as did the predicted probability of observing a statistically significant difference.

Figure 4. Trajectories of ADAS-Cog When Targeting Amyloid in Prodromal AD



Trajectories of the median and interquartile range across replications of mean of ADAS-cog score by arm. Simulation of anti-amyloid treatment in a population with prodromal AD.

Discussion

CTS can provide valuable insights when designing and interpreting AD trials. A disease model makes explicit the relationships between components of the disease and the quantitative data that underpins those relationships. In the analysis presented here, CTS was used to evaluate a trial protocol similar to that of EXPEDITION 3 and to explore the implications of different hypotheses of the disease pathology that have emerged from that and related trial results. The simulation predictions were consistent with the observed trial results, suggesting it was unlikely to show a statistically significant difference in ADAS-cog in a population with mild AD. This prediction reflected both the specific treatment effect assumed and the patient population treated. When a more potent treatment effect was hypothesized, affecting both amyloid and tau pathology, the predicted likelihood of success rose dramatically. Similarly, consistent with current thinking that amyloid targeting therapies may be more effective in earlier stages of the disease, the model estimated a high likelihood of success in a trial of people with prodromal AD, particularly over longer treatment periods.

Overall, CTS provides a means to quickly and affordably explore AD trial design options using limited clinical information before drug testing. CTS can provide quantitative context for decisions regarding trial parameters, such as inclusion and exclusion criteria, subpopulations, and primary and secondary endpoints. At the completion of a trial, CTS can also offer insight into the consistency of specific biological hypotheses with the trial results and the implications of those hypotheses for future decision making. With advances in disease simulation and clinical trial simulation, CTS is beginning to reach the promise identified by the U.S. Food and Drug Administration (FDA) in the 2006 Critical Path Opportunities Report, that CTS "could reduce the risk and cost of human testing by helping product sponsors make more informed decisions on how to proceed with product testing and when to remove a product from further development."[1,9] ■

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[8] Doody RS, Thomas RG, Farlow M, et al. Phase 3 Trials of Solanezumab for Mild-to-Moderate Alzheimer's Disease. *N Engl J Med.* 2014 Jan 23; 370(4):311-21. doi: 10.1056/NEJMoa1312889.

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Strategic Evidence Generation Planning for Optimal Product Positioning

Teresa Wilcox

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In this turbulent global economy, fraught with increasing regulatory requirements and impending legislative changes, obtaining optimal product positioning and market uptake requires thoughtful planning and a fresh perspective. The crowded therapeutic marketplace has driven the need for product differentiation and comparative assessment, and formulary decision makers and payers are demanding greater quantities of evidence with an increasing level of scientific rigor. It is now more critical than ever that pharmaceutical and medical device manufacturers seek to answer the tough questions that will define product value. These questions may include, but are not limited to:

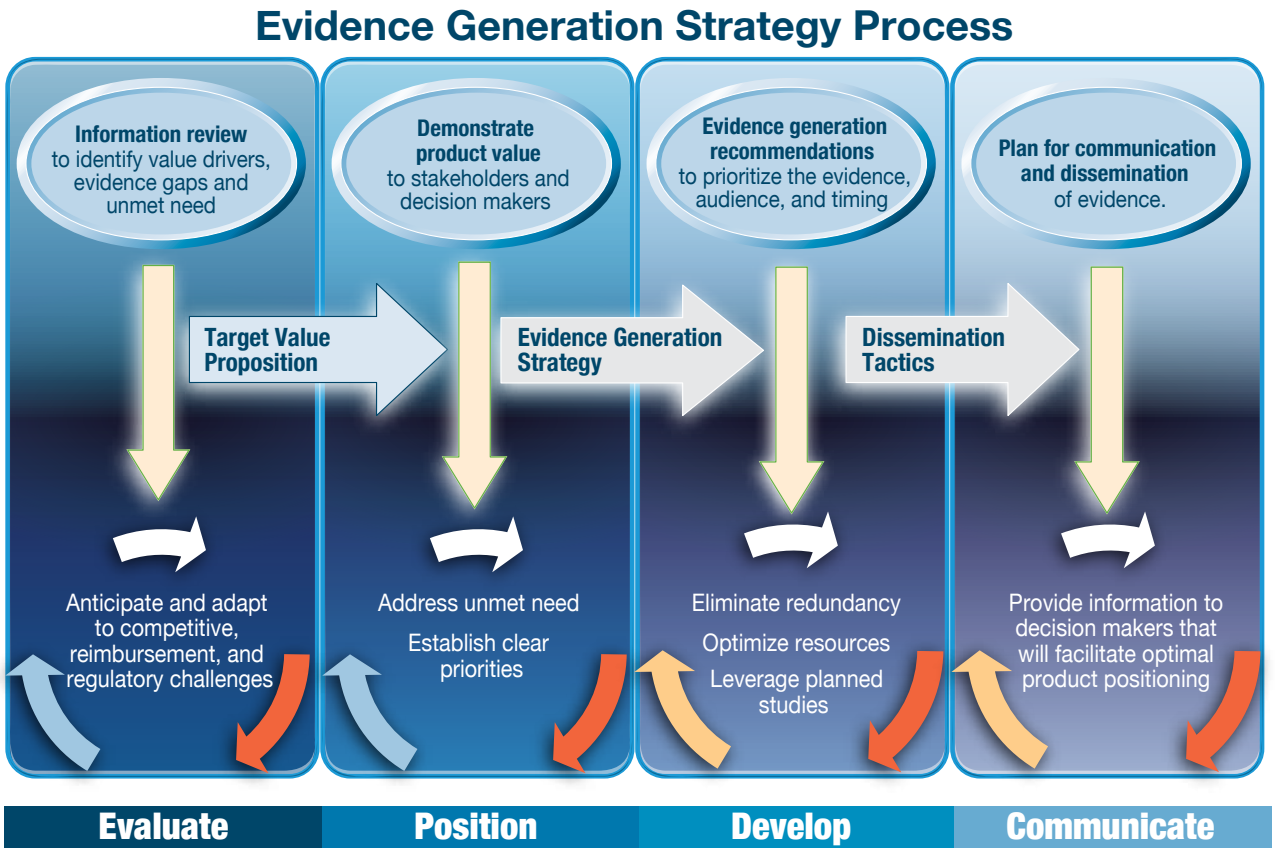
- Do you understand the unmet need in the marketplace, and are you leveraging the clinical endpoints and appropriate evidence to address it?
- What are the critical thresholds for evidence that must be met to enable decision making?
- Are you aware of the competitive, regulatory, and reimbursement environments, both present and future, and is your product development strategy designed accordingly?
- Do you understand the evidence-based value profile required by all relevant customer groups for optimal product positioning?
- Do your product development/commercialization plans mitigate risk while also ensuring maximal market adoption?

Although often complex and challenging in the face of resource limitations, effectively answering these questions requires a comprehensive, multi-year, multidimensional strategy to document and communicate evidence of product value. Employing a strategic evidence generation approach will facilitate coverage, reimbursement, and adoption by ensuring that the ***right value-based evidence*** is communicated to the ***right audience*** at the ***right time***.

Strategic evidence generation, as an approach, is a results-oriented process that assures available data are fully leveraged, new research projects are carefully designed to build a unified body of evidence, and information is effectively communicated to key decision-makers. It is most effective when a systematic, standardized, and repeatable process is in place, and when properly implemented, it will result in efficient demonstration of product value. Typically, this approach will include the following four key steps:

- Identify, summarize, and evaluate the available evidence, the marketplace (i.e., standards of care, comparator treatments, key stakeholders, etc.), and competitive challenges to identify evidence gaps and unmet need.
- Determine the target value proposition that addresses unmet need and describes (or demonstrates) product value to internal stakeholders and external decision makers.
- Identify and prioritize the evidence required to support the target value proposition, define the

Graphic 1: Strategic Evidence Generation Planning Process



resources needed, and outline a timeline for evidence generation.

- Outline a publication plan and communication strategy to ensure that the ***right evidence*** reaches the ***right audience*** at the ***right time***.

Opportunities for Strategic Evidence Generation as an Approach

Central to effective strategic evidence generation is the need to first understand the characteristics and target indications of the product, and its place and progression through the development lifecycle. Generally speaking, this approach may be applied to pharmaceutical, medical device, or diagnostic products spanning the entire product development lifecycle.

- **Early stage preclinical development:** A strategic evidence generation approach may be employed as a vehicle to set the stage for go/no-go due diligence decisions, prioritize information gathering on disease burden and competitive landscape, and inform the product value story as well as the clinical trial study design and implementation.
- **Mid-phase clinical development (successful proof of concept):** This approach can be used to define and prioritize evidence generation tasks, align internal stakeholder audiences, as well as describe tactics to address competitive, regulatory, and market access hurdles.
- **Marketed products:** Strategic evidence generation may be used to leverage or expand upon existing evidence, revitalize an underperforming product (increase market uptake), or respond to new competitive challenges, new information, or changing market dynamics.

Why is Strategy Important for the Generation of Evidence?

The delivery of the right evidence to the right audience at the right time empowers evidence-based coverage decisions that foster ***optimal product positioning***. The design of a comprehensive evidence generation strategy enables one to understand and adapt to the changing world economy, healthcare legislation, and regulatory and reimbursement policies, thereby ***anticipating competitive challenges*** and changes in market dynamics.

Strategic evidence generation is foundational and will serve to establish clear priorities and ***maximize efficiency*** of product development by eliminating redundancy and streamlining efforts across internal groups, thereby optimizing resource allocation and providing

Table 1. Product Challenges and Evidence Generation Opportunities by Phase

PRODUCT	POTENTIAL CHALLENGE	EVIDENCE GENERATION STRATEGY OPPORTUNITY
Early Stage – Preclinical Development		
In **Preclinical** or **Phase I** trials – very little known about the product and the marketplace	Making an informed decision for allocating resources for further product development	• Enable go/no-go due diligence decisions • Prioritize information gathering on disease burden and competitive landscape • Inform product value story and clinical trial study design and implementation
Mid-phase Clinical Development – Successful Proof of Concept		
In **Phase II** or **early Phase III** – may have multiple indications, submission dates, target countries/ markets, etc.	• New data/trials required for Food and Drug Administration (FDA), European Medicines Agency (EMA), or other regulatory agencies - delaying submission and providing opportunity for change in competitive landscape • Entering a crowded, competitive, and controversial market • Obtaining optimal positioning and market uptake when internal competitors exist	• Navigate competitive, regulatory, and market access hurdles • Define evidence generation tasks to position and support product launch • Leverage clinical trials and other studies in progress • Identify and establish payer/stakeholder audiences and internal priorities for launch
Approved and Marketed		
Phase IIIb/IV, or **Phase III** trials underway for a new indication or formulation	• Payer resistance if currently available formulations or comparators are well established, and available at a low cost • Underperforming product or competitor product • Crowded marketplace; available generics • Effectively communicating improvements in compliance and associated cost savings	• Define evidence generation tasks, including real-world evidence, to ensure optimal positioning and market uptake alongside other formulations and products in company portfolio • Leverage body of existing evidence, and any clinical trials or studies in progress • Integrate new evidence into current marketing strategy • Respond to competitive challenges and changing market dynamics

opportunities to leverage planned studies and available resources. This approach also focuses and informs decision making for early stage products in development.

Considerations for Effective Strategic Evidence Planning

The key elements of an effective strategic evidence generation plan are 1) senior scientific expertise, 2) a proven approach, 3) solutions-oriented, communication-focused recommendations, and 4) an emphasis on the evidence. Scientific expertise should include both therapeutic and methodology expertise (e.g., epidemiology, market access, modeling, outcomes research), in addition to an established understanding of regulatory agencies and formulary decision makers, such as health technology assessment agencies (HTAs) and payers. Any truly valuable evidence plan will succeed in aligning internal teams and ensure that all groups are communicating and leveraging the work that others are doing. Transparent working relationships with vendors (e.g., partnership is desirable in lieu of standard contract service), and strict adherence to timelines and deadlines are also critical elements.

Once completed, the plan should emphasize the ability to demonstrate effectiveness, manage safety risks, and document product value. In order to accomplish this, it is imperative that evidence development recommendations are not solely driven by capabilities or available resources, but instead are solution-oriented, evidence-driven, communication-focused, and effectively aligned with messages and audiences.

When implemented properly, a strategic approach to evidence generation provides a comprehensive, multi-year strategy across the product lifecycle to document and communicate evidence of product value. This systematic approach allows for thoughtful planning of evidence generation and associated resource allocation to optimize product positioning. In others words, an evidence generation strategy provides the ability to generate the ***right value-based evidence,*** for the ***right audience,*** at the ***right time.*** ■

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Using Real-World Evidence in Payer Negotiations
What's in Your Playbook?

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Introduction

Rapid payer formulary acceptance with minimal restrictions can accelerate uptake, supporting successful product launch and commercial success. Similarly, maintaining or even expanding patient access to your product against competitors provides continued success for the product prior to loss of exclusivity. Regardless of your scenario, the generation and strategic use of real-world evidence (RWE) plays an important role in acquiring – and defending – optimal payer position, thereby enhancing return on investment.

However, not all RWE is created equal, and defining the strategy that can support a strong case for your product is dependent on a number of factors, including but not necessarily limited to the following: 1) where the compound is in terms of product lifecycle (e.g., early clinical, ready for launch, post-launch); 2) insight into the disease environment and relevant patient characteristics; 3) the competitive environment including the characteristics and performance of your competitors' products; and, 4) a strong position on how your product offers differentiated clinical, economic, and/or humanistic value. While RWE can provide value at all stages of the product lifecycle, in this article we provide some examples from our playbook that demonstrate how it can be used to align with payers on environment and value versus competitors at launch; defend payer positioning; and potentially even bolster and extend the value of on-market products.

"In order to establish a baseline for constructive communication and negotiation, it is important that the manufacturer and payer develop a shared understanding and agreement on key elements of the playing field... "

Readying for Launch: Establishing the Playing Field

Manufacturers need to prepare for negotiations with payers involving the value of a new product; formulary position, restrictions, and management; and, financial impact, discounts, rebates, or other contract elements. These negotiations are intense at launch, and the conversation is continued across the lifecycle as the funding environment changes, contracts are considered for renewal, or new data or new products are introduced that could impact market access.

In order to establish a baseline for constructive communication and negotiation, it is important that the manufacturer and payer develop a shared understanding and agreement on key elements of the playing field, such as (but not necessarily limited to): definition(s) of

the population(s) of interest, treatment(s) of interest, and outcome(s) of interest. Without a common understanding of, and agreement on, the current environment, manufacturer communication on product value may not be understood or appreciated. While this seems straightforward, there are a number of reasons why a payer's perception of the current environment may differ from that of the manufacturer, including differences in definitions and methods. Moreover, information shared with the payer will likely only resonate to the degree that it reflects their particular population. As a result, manufacturers may struggle to convey their product's potential to positively impact that baseline environment. Without clear, common, and accepted methods applied to the unique population covered by the payer, the limited time available for face-to-face discussions may be spent primarily on attempts to understand and resolve differences in methods or differences in the payer's population, rather than share information on the new product's value.

RWE provides a perfect opportunity for manufacturers to help payers appreciate the burden of disease in their "unique" population, and to understand how the manufacturer's product may benefit their patients, providers, and/or bottom line. One potential method by which this can be accomplished is by offering to serve as a research partner. Specifically, by proactively developing study protocols and/or statistical analysis plans that include a detailed description of the sample selection process, explicit definitions for all operational measures, and a means by which data should be output (e.g., table and figure shells), the manufacturer can provide an individual payer with the means to generate RWE that is specific to their population *and* focused on case definitions and operational measures relevant to the product. Once the playing field is established by these prespecified methods, subsequent conversations between the manufacturer and the payer can then focus on any and all of the following:

- The incidence/prevalence of the condition within the payer's specific population;
- The current burden of illness/magnitude of unmet need among these patients that highlights items of key relevance to the product's value proposition;
- Treatment patterns (including but not necessarily limited to adherence, persistency, discontinuation, and/or switching among particular products/classes);
- Safety of particular competitor products; and/or
- Comparative effectiveness (limited to instances where the product is already available).

By removing issues of methodology from the equation, the manufacturer can focus attention on what is of key interest – identification of the magnitude of a potential health issue and the extent by which it can be addressed by access to a newly launched product (or expanded access to an existing one).

Going on the Offensive/Playing Defense with RWE

Established competitors with an entrenched position and/or established financial incentives can create market stasis; other challenging issues for manufacturers include (but are by no means limited to) clinician attitudes stemming from confidence borne of hands-on experience, prevailing treatment guidelines that list competitors as preferred treatment options, and/or other disease-specific issues (e.g., antimicrobial stewardship). Without (and even sometimes with) price concessions, it can be difficult to overcome payer and/or clinician inertia and obtain market access that is minimally constrained.

Successful payer negotiations for a new product can be supported by identifying the economic and clinical limitations of current established products that could be offset by the new product's value proposition. Real-world evidence is a key means by which to identify and disseminate these limitations, as established products may perform different in clinical practice than they do in clinical trials for multiple reasons. Some of these reasons may in fact create risk for the established drug and aid in building the case for unmet needs the new product could address, including the following:

- The population studied in the trial is unlikely to perfectly mirror the population that ultimately takes the drug. Among other factors, patients may be older, sicker, or have more comorbidities, all of which may impact the outcomes achieved and even tolerability of the drug in practice, creating opportunities for improvement.
- Similarly, the established product may demonstrate weaker performance in a specific population (e.g., with a certain biomarker, comorbidities, disease status) where a novel product performs particularly well.
- The established product may result in levels of utilization and cost of healthcare resources that are greater than expected.
- Safety monitoring in trials is unlikely to uncover all adverse events that occur, and may not fully reflect associated resource utilization/cost to the payer.
- As patients are typically followed less closely in real life than during a clinical trial, they may be less adherent to medications, resulting in suboptimal dosing. With potentially less-frequent exposure to

healthcare practitioners, patients may engage in less optimal behaviors, influencing outcomes negatively. While a novel product may face similar risks, different routes of administration and/or dosing regimens (including long- versus short-acting agents) may inherently reduce the risk of suboptimal dosing.

Alternatively, a clinical trial may be powered for non-inferiority, which is sufficient grounds for regulatory approval but does not provide payers with clear guidance as to which patients merit access to the newly approved product (versus "non-inferior", and potentially less expensive, comparators). The latter issue is especially problematic if the manufacturer did not include economic endpoints in their trial(s) that may provide differentiation between products.

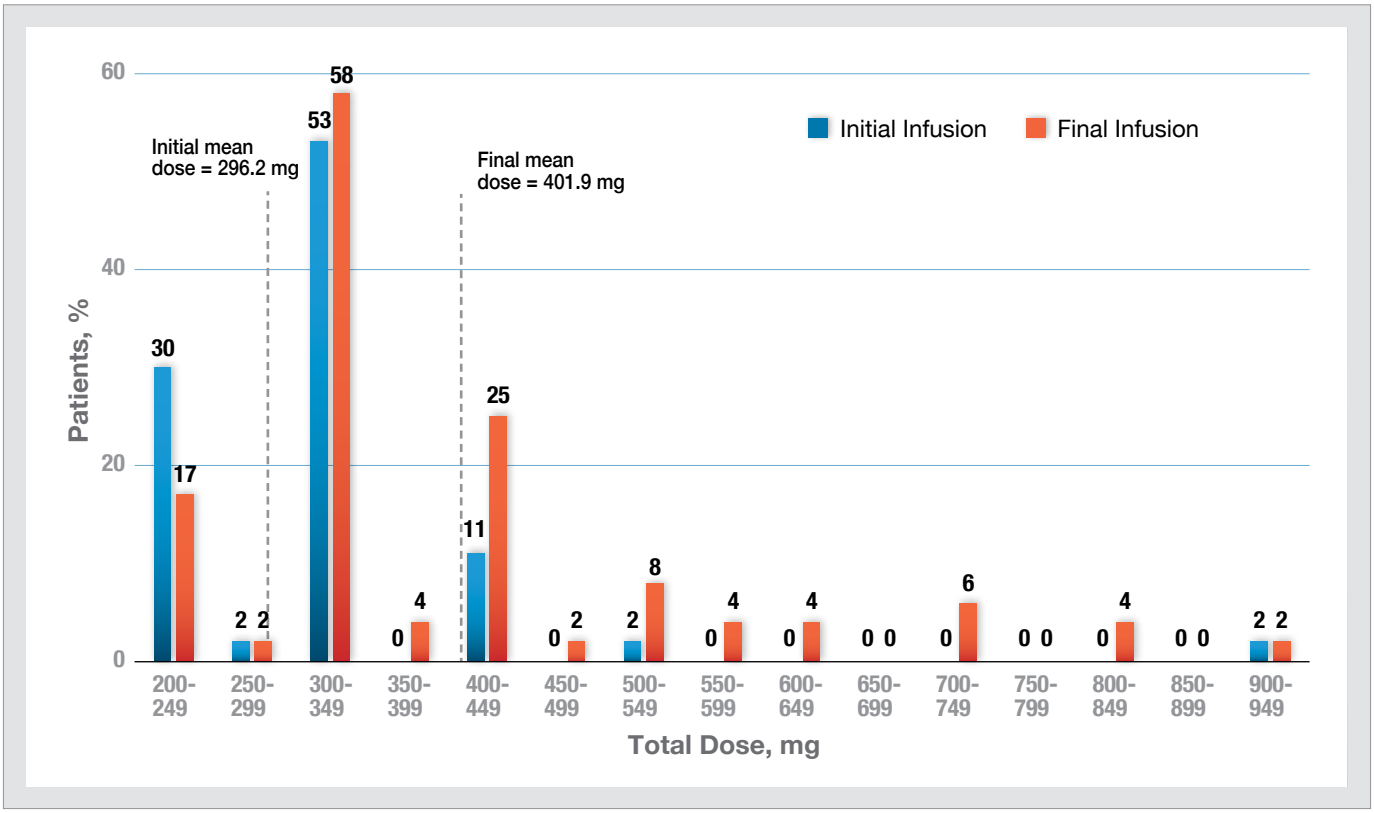
Once your product is in the established position, planning ahead can help prepare you to defend its position from new entrants. Naturally, some of the same vulnerabilities you identified in competitors at launch could apply to your product once marketed and used. Strategic use of RWE can potentially support maintaining or even improving your access over time, and in the face of competition.

Some of the potential opportunities to defend or expand position for an established product include:

- Proven impact on "hard" outcomes such as reduced event rates (e.g., mortality, costly events such as surgeries or hospitalizations) versus surrogates measured in trials. These can be more powerful if there are key differences to novel products, such as mechanism, that would call into doubt whether similar impact on surrogates of the novel drug would have similar outcomes.
- Evidence of value in high-risk or difficult-to-treat populations that might not have been studied in trials, or where there might not have been significant data
- Evidence of reduced use and/or cost of healthcare resources
- Evidence of long-term safety
- Evidence of strong adherence that in turn is associated with positive outcomes

Some examples of the use of RWE for these purposes from our own personal experiences are provided below. One such example where actual drug utilization significantly exceeded utilization expected based on package inserts (and by extension, trial data), creating higher drug costs but also uncertainty on safety and outcomes, is a previous examination of patterns of use of infliximab (Remicade®) among patients with rheumatoid

Figure 1. Frequency Distribution of Initial and Final Dose of Infliximab



arthritis (RA) identified in a large U.S. healthcare claims database. In this study, a total of 53 patients with RA were identified who initiated therapy with infliximab between January 1, 2000, and September 30, 2001; the date of initiation of infliximab was designated the index date, and attention was focused on patients who received infliximab for at least 1 year subsequent.[1] The authors contrasted "real-world" use of infliximab over the 1-year period following the index date – in terms of the number of infusions of infliximab received and corresponding doses thereof – with recommendations set forth in the package insert. Over the 1-year study period, 28% of patients received >8 infusions (based on package labeling current at the time the study was undertaken, patients with an adequate response to infliximab should receive 8 infusions of such therapy over 1 year). The mean dose of infliximab increased from 296.2 mg during the initial infusion to 401.9 mg at the final infusion *(Figure 1)*. While patient weight was unavailable in the data, calculations done by the authors based on the average weight of persons with RA in the U.S. suggested that the initial dose of infliximab was closer to 4 mg/kg than the recommended starting dose of 3 mg/kg. Dose increases were common – one-half and one-third of patients experienced dose increases between their initial and final infusions of ≥30% and ≥50%, respectively. Taken collectively, this study indicated that in clinical practice, physicians initiate infliximab at a dose higher than suggested by the package insert and frequently increase dose and/or number of administrations over the course of the first year of therapy, despite the corresponding increase in risk of adverse events. Accordingly, findings from this study could potentially be used to highlight potential concerns associated with use of infliximab for RA, based exclusively on RWE.

Spotlight on Relevant Subgroups

Another set of examples come from examinations of use of various medications among elderly patients (i.e., age ≥65 years) with painful neuropathic disorders (PNDs) and generalized anxiety disorder (GAD), respectively; the former was assessed in a U.S. database and the latter in a German database. Causes of PNDs are varied, and include diabetes, infection with herpes zoster, acquired immune deficiency syndrome (AIDS), and nerve compression and entrapment syndromes. Their treatment is difficult, as the effectiveness of opioids and other "traditional" analgesics is limited; typically "adjuvant" analgesics such as antiepileptics and antidepressants are required. GAD, which is a chronic disorder characterized by persistent worry or anxiety more days than not for ≥6 months, is the most common anxiety disorder among patients presenting to primary care physicians.[2,3] Several different medications are used to treat GAD, including benzodiazepines (which have long been considered the mainstay of therapy), buspirone, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and venlafaxine.

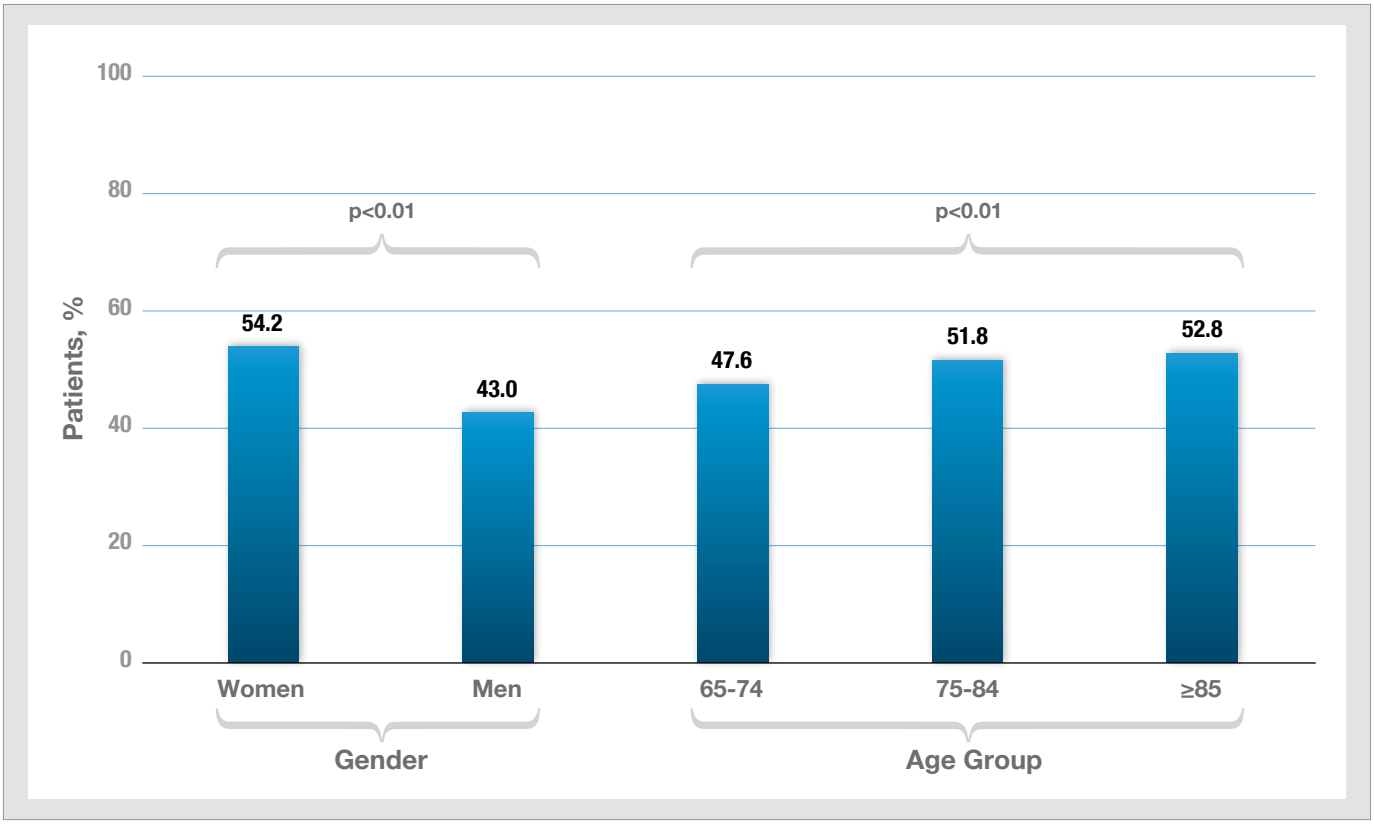
Table 1. Potentially Inappropriate Medications Used to Treat PNDs and/or GAD

Medication	Used to Treat PNDs	Used to Treat GAD
Indomethacin	Yes	No
Opioids	No	No
Propoxyphene and propoxyphene combination products	Yes	No
Pentazocine	Yes	No
Meperidine	Yes	No
Skeletal muscle relaxants		
Methocarbamol	Yes	No
Carisoprodol	Yes	No
Chlorzoxazone	Yes	No
Metaxalone	Yes	No
Cyclobenzaprine	Yes	No
Tertiary tricyclic antidepressants		
Amitriptyline	Yes	Yes
Chlordiazepoxide-amitriptyline	Yes	No
Perphenazine-amitriptyline	Yes	No
Doxepin	Yes	Yes
Benzodiazepines*	Yes	Yes
Meprobamate	Yes	No
Hydroxyzine	Yes	Yes
Promethazine	Yes	No

*Lorazepam, oxazepam, alprazolam, flurazapam, temazepam, zolpidem, chlordiazepoxide, chlordiazepoxide-amitriptyline, diazepam, bromazepam, lormetazepam, nitrazepam, oxazepam, tetrazepam, triazolam, chlorazepate, flunitrazepam, flurazepam, halazepam, medazepam, nordazepam, prezepam

As patients age, their ability to metabolize medications decreases. In 1997, a panel convened by Mark Beers identified a number of medications that were deemed "potentially inappropriate" for use in elderly patients irrespective of indication or place of residence (e.g., nursing home versus community), and that were limited to agents with greater potential for harm than benefit.[4,5] These criteria, which were subsequently updated by Zhan,

Figure 2. Use of Potentially Inappropriate Medications among Elderly Patients in the US with PNDs



et al. to possibly allow for some instances where these medications may be appropriate (i.e., drugs that should always be avoided, drugs that are rarely appropriate, drugs that are appropriate for some indications)[6] include a number of different medications commonly used to treat pain and/or GAD *(Table 1)*. While the criteria are not without their limitations, they have often been used to assess potential safety risks associated with medication prescribing among the elderly.[6-14]

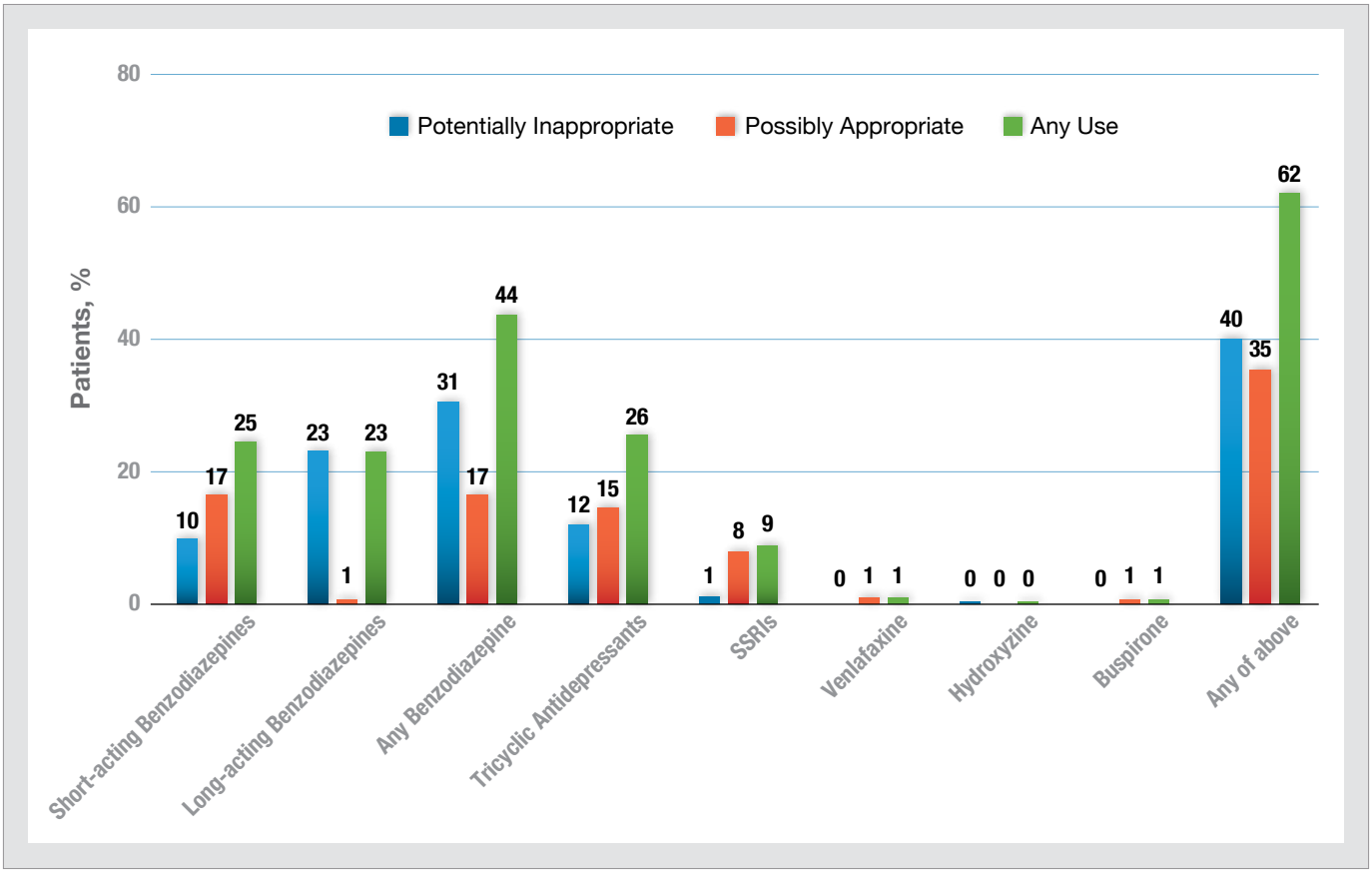
Using a large U.S. healthcare claims database, a total of 22,668 elderly patients with PNDs were identified during 2000; nearly one-half (49.6%) of patients received at least one potentially inappropriate pain-related medication during the year.[15] Women were more likely than men to receive such medications, and use increased with age (p<0.01 for all comparisons) *(Figure 2)*.

"Taken collectively, results of these studies suggest that in multiple markets, the prescribing of potentially inappropriate medications to elderly patients with chronic, often debilitating, conditions is a relatively common phenomenon."

Using a German database with information from encounters with general practitioners (GP), a total of 975 elderly patients with GAD were identified between October 1, 2003, and September 30, 2004; 40% received at least one potentially inappropriate medication during the year, including long-acting benzodiazepines (23%), short-acting benzodiazepines at relatively high doses (10%), and tricyclic antidepressants (12%).[16] Unlike the PND study described above, the authors classified receipt of medications as potentially inappropriate or possibly appropriate, based on the aforementioned updated criteria from Zhan, et al. and information on daily dosage contained within the database *(Figure 3)*.

Taken collectively, results of these studies suggest that in multiple markets, the prescribing of potentially inappropriate medications to elderly patients with chronic, often debilitating, conditions is a relatively common phenomenon. While the precise reason(s) underlying observed prescribing patterns are not discernable from the data sources used, it is likely that contributing factors include clinician familiarity with the products (benzodiazepines and propoxyphene were first approved decades previously), acquisition cost (many of the products on Beers' [and subsequent authors'] lists

Figure 3. Use of Potentially Inappropriate Medications among Elderly Patients with GAD in Germany



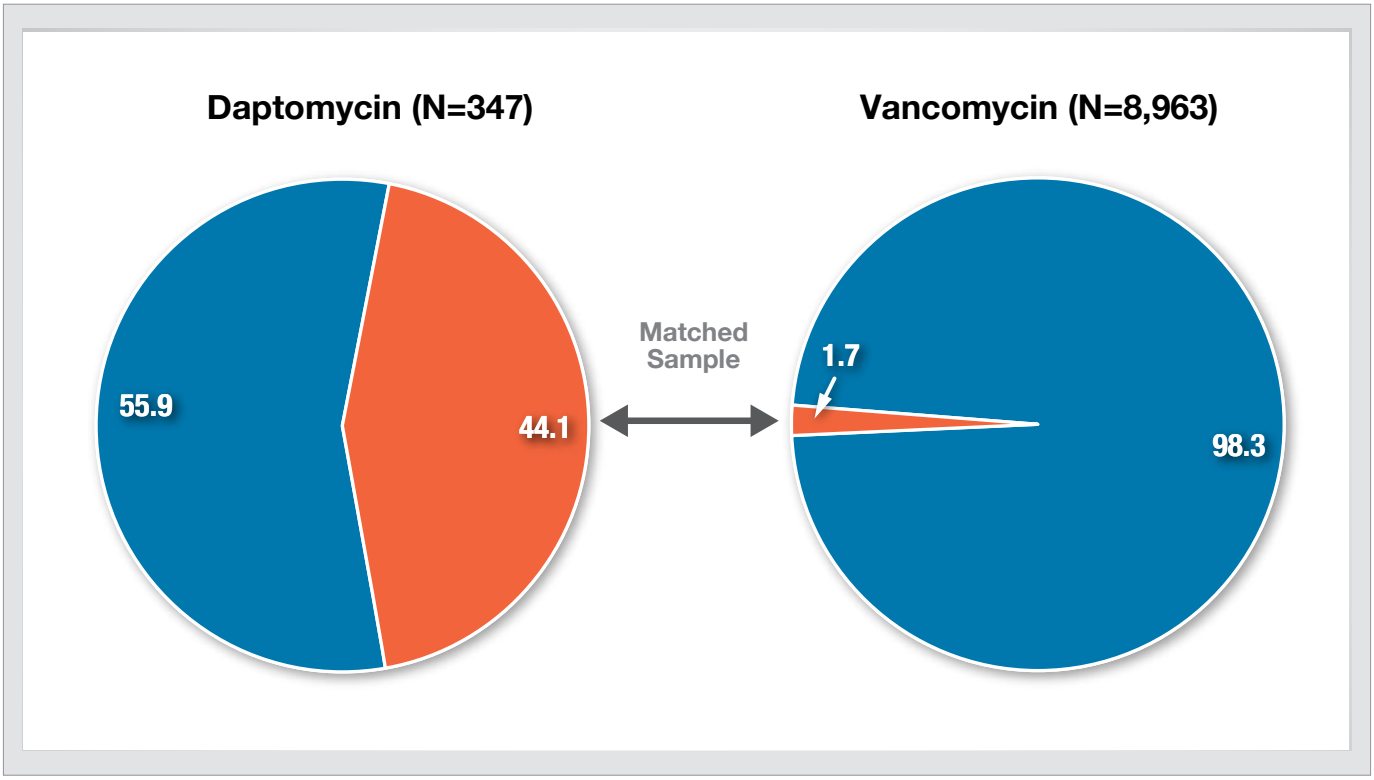
are available as generic preparations), and published treatment guidelines that do not differentiate suggested treatments by patient age (benzodiazepines, buspirone, TCAs, and SSRIs are all recommended for GAD,[17-19] with no distinction made for age). While clinical and economic consequences associated with prescribing of these potentially inappropriate medications were not assessed in either study, it stands to reason that this RWE, coupled with education on alternative medications with demonstrated efficacy in PND or GAD and relatively favorable safety profiles among the elderly may give providers and/or payers reason to entertain arguments in favor of relatively safer alternatives in this "at-risk" population.

Elevating the Game

While RWE is used to inform payer negotiations and help support market access decision making, a limiting factor can be access to appropriate data. After all, your evidence is only as good as the data upon which it is based. While many questions – especially those in support of products currently on the market – can be addressed using existing data sources, such as healthcare claims, electronic medical records (EMR), chart reviews, and/or encounter databases (hospital- or physician-based), there are times when such sources cannot be leveraged. Reasons that preclude use of these sources are somewhat varied, but tend to focus on one of two issues – the source does not contain the information necessary to address the question (e.g., traditional claims data lack patient-reported outcomes, reason[s] for prescribing, or detailed clinical measures) or the concern that comparisons of interest suffer from potential confounding data that cannot be addressed from available information. As the former is fairly self-explanatory, we will focus our final example on the latter.

Complicated skin and skin-structure infections (cSSSI), which are commonly caused by methicillin-resistant *Staphylococcus aureus* (MRSA), typically require admission to hospital and use of parenteral antibiotic therapy. While vancomycin is considered the "workhorse" in this area for a number of reasons (e.g., physician familiarity [it was approved in the 1950s], low acquisition price, place in treatment guidelines, concerns around antimicrobial stewardship), it may not always be the optimal choice. Newer agents (e.g., linezolid, tedizolid, daptomycin, ceftaroline, dalbavancin, oritivancin) may offer additional benefit (e.g., reduced dosing schedules potentially reducing or even precluding admission to hospital, easier parenteral-to-oral conversion thereby optimizing adherence post-discharge, reduction in risk of

Figure 4. Distribution of Matched and Unmatched Patients



development of vancomycin-resistant S. aureus [VRSA]) albeit at higher acquisition prices). Further complicating the issue is that Phase III clinical trials of antimicrobials are typically powered for non-inferiority (as opposed to superiority), which limits the usefulness of data generated during the clinical development program in supporting arguments in favor of expanding market access for the newer products.

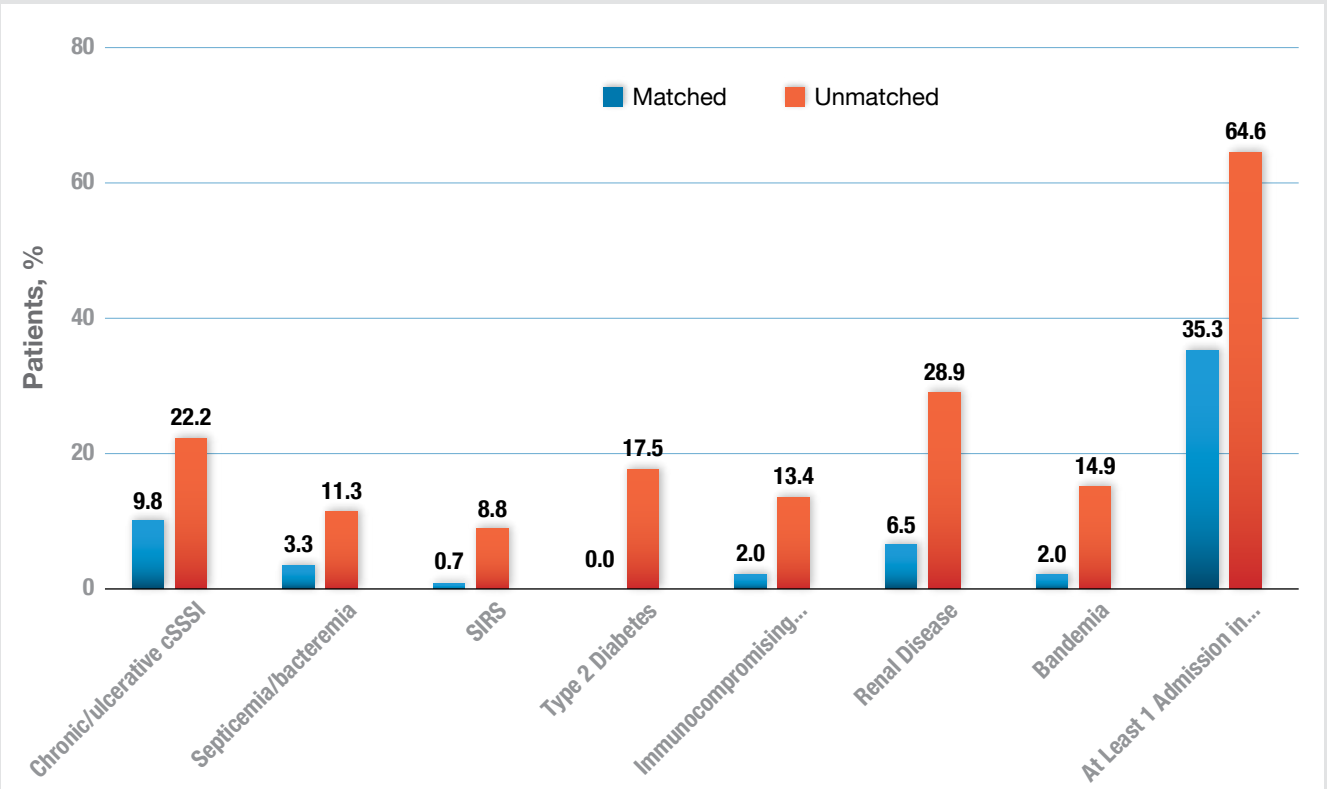
Could RWE based on existing data be used to support arguments in favor of use of newer products? In a prior study that sought to compare selected outcomes and costs among cSSSI patients treated with vancomycin versus daptomycin,[20] a total of 9,310 admissions to hospitals involving use of vancomycin or daptomycin as initial antibiotic therapy for cSSSI between January 1, 2007, and June 30, 2010, were identified in a large U.S. hospital database; 8,963 patients (96% of the study sample) received initial therapy with vancomycin. Interestingly, four hospitals contributed 54% of daptomycin cases, but only 17% of vancomycin cases; the hospital with the largest proportion of daptomycin cases (28% of all such patients) contributed only 4% of vancomycin cases. As the demographic and clinical characteristics of daptomycin patients differed from those of vancomycin patients, the former were matched to the latter on the basis of propensity scores. However, while propensity-score matching led to clinical equipoise between the groups, it also resulted in the exclusion of more than one-half of daptomycin patients and nearly all (98%) vancomycin patients for whom matching could not be done *(Figure 4)*. Paradoxically, in order to maximize internal validity by controlling for observed selection bias that would confound comparisons of the two agents, most "real-world" patients treated with either antimicrobial were *excluded* from the study, thereby threatening external validity.

"Unlike clinical trials ... the purpose of a pragmatic trial is to establish effectiveness of interventions in real-world settings."

Patients for whom matching was successful also differed substantially from their unmatched counterparts – specifically, matched daptomycin patients were younger (mean age = 52 years vs. 57 years for unmatched patients); they also had different types of cSSSI, were less likely to have clinical markers for severe infection, and were less likely to have comorbidities ($p<0.01$ for all comparisons) *(Figure 5)*. Similarly, matched vancomycin patients tended to be relatively sicker than their unmatched counterparts (data not shown).

The generalizability of the resulting sample to all real-world cSSSI patients treated with daptomycin versus

Figure 5. Characteristics of Matched and Unmatched Daptomycin Patients*



*p<0.01 for all comparisons

vancomycin was unknown and likely low due to the relatively small number of patients for whom matching could be done and the fact that analyses would be limited to the "worst" cases treated with vancomycin versus the "best" cases treated with daptomycin (i.e., use of daptomycin as first-line therapy in the "real world" appeared for the most part to be focused on different patients than those for whom vancomycin was used). Moreover, despite matching, substantial concerns remained around selection bias (i.e., residual confounding) at the physician and/or institution level that could not be addressed with information available in the database. In instances like this – and those for which existing data do not contain the information necessary to conduct the appropriate comparisons – alternative study designs such as pragmatic trials are required. Unlike clinical trials, which focus on ascertaining the efficacy of an intervention in well-defined settings that are designed to control for all known biases/sources of confounding, the purpose of a pragmatic trial is to establish effectiveness of interventions in real-world settings. Accordingly, pragmatic trials tend to embrace an "all comers" approach, and use as comparators other "active" interventions in order to address the policy question as to whether current thinking on appropriate treatments should be changed. While not without their own challenges, in instances where existing data are unavailable/found insufficient to address your needs, these designs allow for the analyses required to generate the RWE necessary to influence payers to gain, retain, and/or expand market access.

Conclusion

Across the product lifecycle, a delicate and never-ending game is played between manufacturers and payers. While both sides share a common goal of improved patient health, reduced physician burden, and decreasing burden of illness, they tend to differ on their approach. Developing a playbook that sets forth your approach to the generation of RWE that can support your product's value and differentiation can enhance and accelerate payer negotiation and improve total lifecycle revenue. Appropriate and timely use of RWE has the potential to help you ground payer discussions in the specific dynamics of their population of interest (within a specific country or health plan), aligned with treatment patterns and resource use that occur within their purview. For manufacturers, the result of these conversations is to move the game to their playing field, potentially creating greater impetus to value products – and by extension – winning the game by gaining and ultimately expanding provider and patient access to their products. ■

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Clinical Outcomes Assessments
Unique Considerations in Pediatric Rare Diseases

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Researchers are often asked to make recommendations for strategic protocol development for clinical trials for rare diseases, to create evidence dossiers to support regulatory filings, and to design studies to assess validity or reliability for clinical outcome assessments (COAs). What makes pediatric rare disease research unique and challenging? How do the challenges impact COA selection and align with the U.S. Food and Drug Administration (FDA) Guidance for Industry on Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims?[1]

The FDA recognizes that there are many challenges in rare disease drug development and that certain aspects that are feasible for common diseases may not be feasible for rare diseases. In 1983, the Orphan Drug Act was established to provide financial incentives associated with orphan drug development designation and to make developing drugs for small numbers of patients financially feasible. Rare diseases without approved treatments may be given fast-track designation to facilitate development and to expedite the regulatory review process. In addition to fast-track designation, a pediatric voucher program is available for expedited review based on surrogate break through designation.[2] Selecting or developing COAs in consultation with the FDA can increase the likelihood of agreement on the content and measurement properties.[3] The FDA has a meeting structure called Critical Path Innovation Meetings that provides a means for patient groups, industry, clinicians, and academics to communicate on key drug development issues, and to improve the efficiency of development and approval. The regulatory approach seems to be having an impact on the volume of emerging studies in rare diseases. Rare disease research is one of the fastest areas of drug development with an average per patient cost of $137,000/year.[4] The percent of pharmaceutical sales is anticipated to increase to 16% of all drug development by 2018, and in 2014, orphan drug approvals represented 37% of all drug approvals. Furthermore, 50% of rare diseases affect children, with 30% affecting before the child's fifth birthday.[4] It is clear that sponsors are reacting to the unmet needs of rare disease interventions. With such an emphasis and the fact that so many rare diseases affect the pediatric population, there is a very clear need for strategic consideration when designing trial endpoints.

The Roadmap to Patient-Focused Outcome Measurement in clinical trials[5] provides guidance on the steps to COA selection or development, but each pediatric rare disease study has unique challenges that need consideration. With this article, we propose using Hypophosphatasia (HPP), to illustrate COA selection in a pediatric rare disease. HPP, a rare genetic metabolic musculoskeletal disorder, is an inborn error of metabolism caused by mutations in the tissue-nonspecific alkaline phosphatase gene, which can manifest in a broad range of symptoms and vary in its severity.[6] Heterogeneous manifestations can include rickets, fractures, muscle weakness, limb deformities, pain, and respiratory compromise, which result in delayed acquisition of age-appropriate

developmental skills, gait impairments, and decreased functional independence in activities of daily living.[6] The disease has a particularly high burden in children and is associated with high mortality rates in infants.[8]

Application to Hypophosphatasia (HPP)

The U.S. Food and Drug Administration approved Strensiq® (asfotase alfa) in 2015 as the first approved drug for perinatal, infantile, and juvenile onset HPP, following development with orphan drug and breakthrough therapy designation. HPP is a rare disease with multi-system impairments, a wide heterogeneity in disease presentation, a small sample size with international site distribution, and natural history literature that had limited functional characterization. The asfotase alfa clinical development plan included multiple studies to evaluate safety tolerability, pharmacokinetics, pharmacodynamics, and efficacy. Targeted clinical trial populations were created by age and functional presentation. The primary efficacy endpoint in all studies was HPP-related rickets as measured by skeletal radiographs. The study endpoint models included secondary and exploratory variables with a combination of patient-reported outcome (PRO), clinician-reported outcome (ClinRO), observer-reported outcome (ObsRO), and performance outcome (PerfO) instruments to provide a comprehensive picture of function, disability, pain, and health-related quality of life (HRQoL). Heterogeneity in functional presentation and a wide range of ages necessitated use of COAs that characterize function relative to normative values. The results highlighted below focus on use of normative values in the infants and children in the clinical trials.

Roadmap to Patient Focused Outcome Measurement in Clinical Trials- Application to Pediatric Rare Disease Research and Hypophosphatasia

Understanding the Disease or Condition	Conceptualizing Treatment Benefit	Selecting/Developing the Outcome Measure
Challenges specific to pediatric rare disease research		
• Literature void of natural history data, especially related to function • Heterogeneity in disease presentation by phenotypes with variable age and functional presentations • A broad inclusion of disease phenotypes allows better characterization for which therapy may be feasible, but adds increased design and analysis complexity • Multi-system impairments • International site distribution with variable standards of care • Developing children have dynamic health states and impacts so static measures are not sufficient to benchmark or assess the target population • Infantile or severe disease presentations may include progressive loss of developmental skills and high mortality with no available treatment	• Concept of interest for infantile presentation is often survival with an open label single arm study design • Conceptualizing benefit by how a child feels and functions is complicated because typical developmental function varies by age and involves a complex interaction between cognitive, communication, and motor skills • Consideration must not only be given to the concepts of interest but also to the interactions between the concepts. Cognition, communication, or attentional capacity may limit ability to measure primary treatment benefit • May be difficult to distinguish between treatment affect and change due to developmental maturation. Identical function may be age appropriate for a younger child and considered atypical or delayed in an older child. In the juvenile form of a rare disease, function may exceed the infantile presentation but the children have multiple co-morbidities and the impact of the impairments need to be measured by comparison to age appropriate task execution, social and peer interaction, and function within the home, school and community environment. • Difficult to develop responder definition with heterogeneity in age and function • Open label clinical trials where patients and investigators are aware of assigned therapy are rarely adequate to support labeling claims based on PRO instruments alone. COAs that support improvement in specific symptoms would not support a general claim related to improvement and multi-domain claims cannot be substantiated by instruments that do not adequately measure the individual disease concepts. Clinical designs often require complicated endpoint models with multiple COA types to capture the constructs ○ Targeted clinical trial populations are desirable for optimal design and ability to demonstrate treatment benefit, but often are limited by recruitment in rare disease and less desirable to have a narrow disease categorization for labeling	• Existing standardized developmental instruments can provide a measure of the impact of multisystem impairment and classify function relative to normative values but; ○ Require extension training for administration often within an international site distribution ○ Challenging to establish disease-specific validation and that conceptual framework is appropriate for study population and endpoint ○ Instrument manuals do not include guidelines for accommodations for special populations, such as strategies to obtain reliable neurocognitive assessments in children that are low functioning, have non-cooperative behavior, or physical disabilities[9] ○ Longitudinal data collection over years may require transitioning between developmental assessments with different psychometric properties ○ Standard scores can be used to discriminate function relative to standard deviations from the normative mean or percentile rank ▪ May not show a treatment benefit (stable or increasing standard score) if new skills are acquired but at a slower rate than the normative sample. Age-equivalent scores may be more useful than standard scores to demonstrate skill acquisition in a child with severe motor impairment[9] • Development of disease-specific validated PROs is challenging due to feasibility, time, and associated costs. ○ In the preschool child, motor skills and level of independence in activities of daily living (ADL) vary greatly by age and require validation of many items and multiple age versions

Understanding the Disease or Condition	Conceptualizing Treatment Benefit	Selecting/Developing the Outcome Measure
Potential strategies		
• Utilize comprehensive prospective, observational, natural history studies with multiple COAs to gain insight into the multi-system impacts on age appropriate markers (symptoms/impacts) • Use these natural history studies to gain insights to the COA performance (sensitivity and specificity) and to look to the relationships between outcome measures (consider language, motor ability, behavioral and cultural aspects) • Characterize disease by distinct age and functional groups using natural history data, KOL's, patient, and caregiver perspectives	• Treatment benefit in the infant population may be defined by global development and the pediatric/ juvenile group may require performance-based or patient-reported assessments that are focused on a specific functional skill that is age specific or disease specific • Treatment benefit may be defined by a responder definition based on acquiring a developmental skill that exceeds function observed in natural history study • Treatment benefit may also be defined by Developmental Quotients (Age Equivalent Scores/Chronological Age x 100) and compared to decline in DQ in the natural history.[9] • Use KOL, focus group, caregiver, and patient perspective to define treatment benefit	• Utilize assessment batteries with normative data for the age and culture being targeted • Utilize disease relevant domains of content within a developmental test • Supplement the batteries with COAs specific to the anticipated treatment benefits • Develop standardized order for all COAs, evaluate areas of overlap between multiple performance instruments to reduce redundancy and subject fatigue • Content validity-establishing evidence that an existing developmental instrument measures concepts of interests in rare disease ○ Highlight validation data used to develop instrument from diseases with similar impairments ○ Complete literature searches to support use in interventional studies with similar impairments ○ Use KOL perspective and consensus meetings to establish disease-specific recommendations for COAs ○ Examine relationship between performance assessments and HRQoL in prospective observation study • PRO instrument development - Use the Patient Reported Outcomes Measurement Information System (PROMIS) item banks to derive items and to expedite the development process. The item banks have already had extensive field testing and are consistent with the International Classification of Function for Children and Youth.[10] • Develop responder definition based on distribution analysis of groups in prospective observation study and expert, patient, and caregiver perspective
HPP example		
• Systematic literature searches and KOLs used to characterize distinct groups by age and function • Retrospective natural history studies completed • Sub-study of larger retrospective natural history study was conducted that assessed gait impairments from clinical gait videos	• Open label, multinational, multicenter, single arm design due to unmet medical need, serious mortality and morbidity risk, and absence of disease-modifying treatment • Multiple studies to measure treatment benefit in infantile, pediatric, and adult onset HPP • Multiple inter-related endpoints in each study that included PROs, ObsROs, ClinROs, and PerfOs	COAs used in Infantile and Pediatric Studies **Biochemical parameters** • Tissue nonspecific alkaline phosphatase enzyme substrates **Skeletal system measures** • Bone mineralization- Biopsy and DEXA • Rickets Severity ○ Rickets Severity Scale ○ Radiographic Impression of Change • Growth **Developmental Function and Strength- Infantile** • Bayley Scales of Infant Development - third edition[13] • Survival – Respiratory Status **Physical Function, Strength and Ambulation –Pediatric** • Bruininks-Oseretsky Test of Motor Proficiency –second edition: Running Speed and Agility and Strength subtests • Hand Held Dynamometry • 6MWT • Modified Performance Orientated Mobility Assessment-Gait (MPOMA-G)[10] **Disability and HRQoL- Pediatric** • Childhood Health Assessment Questionnaire (CHAQ) • Pediatric Outcomes Date Collection Instrument (PODCI)

The Childhood Health Assessment Questionnaire (CHAQ) does not produce normative data but was also included in the summary as a measure of disability and pain. The modified performance-oriented mobility assessment (MPOMA-G) illustrates inclusion of a supplemental instrument to target an age and disease specific area of anticipated treatment benefit.

Bayley-3

The five Bayley-3 developmental domains: cognitive, language, motor, social-emotional, and adaptive behavior were developed (normed and validated) for use in impaired and healthy children between 1 and 42 months of age, and reflect current federal, state, and professional standards for early childhood assessment.[13] The scales have clinical and research utility as a diagnostic assessment for young children with varied disorders and disabilities, and the manual includes strategies to accommodate patients with physical or cognitive limitations. Eleven patients with infantile HPP and an age of 3 years or less were assessed using the Bayley-3 at baseline and at 24 and 48 weeks after initiation of asfotase alfa for treatment of HPP.[6, 8] All patients had fine motor, gross motor, and cognitive delays at baseline and 87.5% of patients for whom data were available showed improvements in these components.[6] Bayley-3 use supported measurement of global development and highlighted that the largest degree of impairment was present in the gross motor subtest. Age-equivalent scores were used to illustrate linear skill acquisition, and scaled scores (mean 10, standard deviation [SD] 3) illustrated rate and level of skill acquisition relative to a normative sample, with median (min, max) Gross Motor scaled scores increasing from 1 (1, 8) at baseline to 2 (1, 5) at Week 48.[14]

Bruininks-Oseretsky Test of Motor Proficiency (BOT-2)

In Pediatric HPP, only the BOT-2 Running Speed and Agility and Strength subtests[15] were utilized because they were the most relevant to the HPP disease-specific impairments and mobility restrictions, and involved a reasonable amount of administrative time when paired with additional outcomes. The BOT-2 provided an opportunity to illustrate that HPP ambulatory function was well below expected values of healthy peers, thus limiting possible patients' participation in the community and school activities. The BOT-2 was used in children 5–12 years of age (N=13) treated with asfotase alfa. At baseline, the median scaled scores for both the BOT-2 Strength and Running Speed and Agility subtests were >2 SDs below the normative mean.[12] Asfotase alfa treatment resulted in significant and clinically meaningful improvements in strength and function, demonstrated by improvements in BOT-2 mean scores to ±1 SD of normal.

Hand-Held Dynamometry (HHD)

HHD is a reliable and easy method to measure muscle strength. In children and adolescents, force values in Newtons are multiplied by limb length to calculate torque, which can be compared with gender-specific norms.[16] In 5 to12 year-old children with HPP, bilateral hip and knee extension and flexion, hip abduction, and grip strength were assessed by HHD.[11] Across muscle groups tested, baseline strength ranged from median 32% (9.4, 52.7) predicted in the hip extensor, to 60% (20.8, 149.2) predicted for grip (reported in torque for the right side as percent predicted for age- and weight-matched healthy peers). With asfotase alfa treatment, strength in all tested muscle groups except grip improved and continued to improve to last assessment ($P<.05$); e.g., a median 83% (45.7, 118.7) predicted was achieved for hip abductor at last assessment.[11]

6-Minute Walk Test (6MWT)

The 6MWT is used to assess the distance a patient can walk on a level course in 6 minutes. The 6MWT reflects an integrated exercise response of multiple systems including the cardiorespiratory, neurological, and musculoskeletal systems and does not isolate the specific system of change. Normative data are available for children and the distance walked can be compared as a percent of the predicted values by age, gender, and weight. In 5 to 12 year-old children with HPP, a rapid improvement with asfotase alfa treatment was demonstrated using 6MWT: the median score increased from 61% predicted at baseline to within the normal range (80–100% of predicted) after 3 months, and remained within the normal range through 5 years of treatment.[17]

Childhood Health Assessment Questionnaire (CHAQ) and Pediatric Outcomes Data Collection Instrument (PODCI)

The PODCI questionnaires include self-report and parent/caregiver reports, with raw scores converted to a standardized scale from 0 to 100, with higher scores corresponding to less disability.[18] Normative scores can also be calculated based on a mean of 50 and an SD of 10. In 5 to12 year-old children (N=13) with HPP receiving asfotase alfa, physical function, ADL, and pain were assessed using the CHAQ[19] and PODCI.[20] At baseline, children had difficulty with upper extremity tasks (e.g., lifting heavy items and pouring a gallon of milk), functional mobility items (e.g., walking, running, climbing stairs, and getting on or off a bus), and participation in community recreation and sports.[20] Decreases in disability and pain were consistent across both measures. Median parent-reported normative PODCI scores for global function (baseline: 27 [-2, 55], ≥2 SD below the normative mean of 50 (SD 10), sports/physical function (baseline: 20 [-13, 53]), and transfer/basic mobility (baseline: 37 [-7, 53])

all improved, reaching normal values (≥44) at 6 months (*P*< .05). The median (min, max) CHAQ disability score decreased from 1.0 (0.0, 2.3) at baseline to 0.0 (0.0, 1.8) at 24 months (*P*=.002). Median PODCI discomfort/pain normative scores improved from below normal (39 [18, 55]) at baseline to a median score of 55 (23, 57; *P*=.055). CHAQ median pain scores decreased from 20.0 (0.0, 72.0) at baseline to 0.0 (0.0, 42.0) at 3 months (*P*=.04).

Modified POMA-G (Performance-Orientated Mobility Assessment- Gait)

The POMA-G is a validated tool for evaluating gait and balance in elderly and community dwelling adults[19] that was modified to capture musculoskeletal impairments that are most relevant to children with HPP.[10] Retrospective clinical gait videos were used to compare the non-interventional natural history group to the interventional group. Children in both groups had gait impairments at baseline and the patients treated with asfotase alfa (8) showed significantly greater improvements (+3.0 [+0.0, +7.0]) compared with controls (6) at last assessment (+1.5 [0.0, 2.0]; *P*=.03; time from baseline to last assessment, 1.7 [0.2, 3.3] and 4.1 [2.0, 5.9] years, respectively).

Conclusion

Pediatric rare diseases present unique challenges in clinical trial design and in selection of COAs that can support claims in medical product labeling. Guidance is not available on best practices to deal with the developing child with cognitive, motor, language, and level of independence in activities of daily living that vary greatly by age. This article illustrates use of multiple COAs with normative data in the HPP clinical trials for asfotase alfa (Strensiq®). Multiple endpoints were required to capture multi-system impacts and to tell the complicated story from biochemical parameters to age-appropriate recreational and community participation. Infants and children on asfotase alfa treatment demonstrated improved bone density, increased strength, and reduced pain; improved functional mobility in age appropriate developmental motor skills and ambulation; reduced disability and increased independence in activities of daily living; improved ability to navigate in the community and school environment; and, increased ability to participate in age-appropriate recreational and community sports. Similar to HPP, many rare diseases present with multi-system impairments and a wide distribution of age and functional levels that are desirable to be included within labeling claims for medical product approval. It is imperative to consider multiple COAs early in the development process to design comprehensive prospective, observational, natural history studies to gain insight into the multi-system impacts on age-appropriate markers. It is also important to consider use of COAs that provide normative data and reflect current standards for early childhood assessment in order to support payer approval and reimbursement for the approved drug intervention and for early intervention services. ■

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Advantages and Disadvantages of Using Phase III Clinical Trials for Psychometric Evaluation of New PROs

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Patient-reported outcomes (PROs) represent one type of clinical outcome assessment that may be specified as primary or key secondary endpoints for clinical development programs of new pharmaceutical or biotech products. The increasing interest in the patients' perspective in understanding treatment benefits and risks requires PRO measures. PROs identified as primary or secondary endpoints for clinical trials need to have adequate evidence supporting content validity and good psychometric properties (i.e., reliability, validity, responsiveness), and have interpretation guidelines. The U.S. Food and Drug Administration (FDA) guidance on PROs for labeling of medical products provides a summary of the evidentiary requirements that the FDA uses to evaluate PROs as endpoints.[1] New PRO measures are developed following a sequence of qualitative research for concept elicitation with patients and clinicians, careful development of item content and response scales, cognitive interviewing studies to ensure respondent understanding and comprehension of the new instruments, and one or more studies evaluating the measurement properties of the new PRO instrument. Ideally, this psychometric evidence is derived from stand-alone observational studies and/or Phase II clinical trials, so that at the initiation of pivotal Phase III clinical trials, information is available on the reliability, validity, responsiveness, and interpretation guidelines for the target PRO measure.

This article briefly summarizes some of the risks and advantages of developing and evaluating the psychometric characteristics and interpretation guidelines within Phase III clinical trials. The summary is based on previous presentations by Johnson, et al.[2] but reflects the perspective of the author and not necessarily the positions of the other presenters.

At times, sponsors and PRO instrument developers need to deviate from the ideal development and psychometric evaluation approach. In the case of accelerated clinical development programs, products for rare medical disorders, and a mismatch between starting the PRO development studies and the clinical development program, the sponsor may be in a situation where the Phase III clinical trial data is needed for the psychometric evaluation. Clearly, there is often a tension between taking the necessary time to systematically develop and evaluate a new PRO measure and interest and progress toward completing the clinical development program as quickly and efficiently as possible. Deviating from the ideal approach for developing and evaluating the measurement characteristics of new PRO measures presents a number of challenges and potential risks for the pharmaceutical industry sponsor.

Basically proceeding with a Phase III clinical trial with a PRO endpoint with unknown psychometric characteristics is very risky. If the PRO is designated as primary or key

secondary endpoint, this approach is riskier than a clinical outcomes assessment (COA) designated as one of several secondary endpoints. Generally, it is not advisable to have a PRO with unknown psychometric qualities specified as primary endpoint.

In some cases, it may be possible to conduct a psychometric sub-study using only part of the overall clinical trial population. However, there may be challenges associated with conducting and maintaining fidelity of a psychometric sub-study, and the sub-study procedures may impact the conduct of the clinical trial. Some of these challenges may be minimized by limiting the psychometric sub-study to well managed and experienced clinical centers. The psychometric sub-study may involve additional clinical and PRO measures, and may require additional clinical center resources. In addition, this approach may result in a reduction in the clinical trial sample that can be used for efficacy analyses (assuming sub-study patients are not included in efficacy analyses). This issue may be minimized by increasing overall sample size to maintain statistical power for efficacy analyses, but also requires an increase in clinical trial expenditures. Regulatory agencies may be concerned about including the psychometric sub-study participants in the clinical trial efficacy analyses. Regulatory agencies may recommend not including the sub-study data in the clinical efficacy analyses because of concern over potential biases. However, it may be possible to include these data in a sensitivity analysis, thus allowing all clinical trial patients to contribute to the efficacy analyses.

There may be increased risk associated with taking the psychometric sub-study approach for determining the reliability, validity, responsiveness, and especially responder definitions for the new PRO. There is always the potential risk that psychometric analyses may demonstrate that the PRO does not have adequate measurement properties (i.e., reliability, validity, responsiveness). This potential risk can be minimized if attention is paid to the concept elicitation and cognitive interviewing stages of PRO instrument development, with the psychometric evaluation confirming that the developers did a good job in constructing the draft PRO measure. In some cases, it may be unknown whether lack of responsiveness is attributable to treatment or the PRO measure. The analyses may find that estimated responder definition criteria is not demonstrated and/or requires larger sample sizes to adequately evaluate responder definitions, often due to inadequate sample sizes for patients improving, remaining stable, and worsening over time.

There are additional specific challenges associated with defining minimal important difference and responder definitions associated with basing these definitions on analyses of Phase III clinical trial data. Ideally, clinical and PRO data from either stand-alone observational studies or Phase II clinical trials are used to evaluate the psychometric characteristics of a new PRO instrument. Basing the clinical responder definitions on data from Phase III clinical trials may result in bias. If the psychometric analyses can be truly masked to treatment status, it may be possible to determine thresholds for clinical responders.

The ideal situation for evaluating responsiveness to clinically meaningful changes in PRO scores and in identifying meaningful responder thresholds for PRO scores is when some subjects are improving, some subjects remain the same, and some subjects are worsening in clinical status over the course of the study. Although basing the responder definitions on clinical trial data is recommended, there may be additional challenges in some cases. For example, in situations where an active treatment is highly effective (e.g., biologic treatments for psoriasis) and there is only a small placebo group, the resultant analyses may inflate estimates of responder definition and responders. In other cases (e.g., congestive heart failure), where the active treatment is not very effective and with small sample sizes, it may be difficult to identify reasonable responder definitions, and these estimates may be attenuated.

"In situations where it is unavoidable to conduct the psychometric analyses based on Phase III clinical trial data, it is essential to mask psychometricians to treatment groups for psychometric analyses of these studies."

In situations where it is unavoidable to conduct the psychometric analyses based on Phase III clinical trial data, it is essential to mask psychometricians to treatment groups for psychometric analyses of these studies. Decisions about item retention and deletion need to be made without reference to treatment group membership. The usual approach is to provide psychometricians with data files without any reference to treatment group status. In addition, no adverse event data is provided, as these data may potentially be used to identify treatment group, especially if there are specific adverse effects associated with the new treatment. The practice is to provide psychometric analysts with only those data files necessary for conducting the planned psychometric analyses.

An innovative approach to handling the masking problem is to set up an independent psychometric evaluation

committee which is tasked with developing and executing the psychometric analysis, much like a data monitoring committee for some clinical trials. The psychometric committee is organized and charged with completing the psychometric analysis masked to treatment group status. The committee can include psychometricians, clinicians and biostatisticians not directly involved with the clinical trial. This committee is masked to treatment group status, reviews psychometric analyses and makes independent decisions about item retention and deletion, domain structure, reliability and validity, responsiveness, and responder definitions for the PRO measures. A report is generated summarizing and documenting these measurement-related decisions for the PRO endpoints.

For regulatory agencies, risks related to reviewing evidence on the psychometric characteristics of new PRO measures intended as primary or secondary endpoints based on pivotal clinical trials are minimal. For example, the FDA will still hold sponsors to standards of evidence summarized in the PRO guidance on PROs[1] regardless of the source of this evidence. However, the FDA may express concern when decisions about final item content, instrument scoring, and especially clinical responder definitions are based on pivotal clinical trial data. There is always the danger associated with unmasking treatment assignments, and in making decisions that may benefit the active treatment under investigation compared with placebo or other comparative active treatments. Regulatory agencies may not be comfortable with the level of evidence for the PRO measure to make confident decisions about the adequacy of the PRO endpoint (i.e., fit for purpose) and the efficacy of the investigated treatment. Regulatory agencies may come under criticism from sponsors and the public for delaying clinical development programs by recommending additional confirmatory PRO development and psychometric evaluation studies. However, unless scientifically sound and adequate evidence on measurement characteristics of the new PRO are available, it is difficult to make informed decisions on efficacy.

There also may be possible risks to patients and the general public associated with PRO endpoints that may not be developed and psychometrically evaluated based on standard approaches. Study participants may be exposed to adverse effects of treatment unnecessarily in clinical trial with inadequate PRO endpoints. For the general public and health care systems, requirements for additional measurement studies to confirm reliability, validity, responsiveness, and responder definitions may delay clinical development programs and providing access to potentially effective treatments. This situation may be particularly troublesome in cases of rare disorders or other medical conditions (e.g., gastroparesis) where there may not be available effective and approved treatments.

In conclusion, deviations from the ideal approach to systematically develop and evaluate the psychometric properties of new PRO endpoints have some risk to the sponsor. These risks can be mitigated somewhat by recognizing these potential risks and developing strategies to minimize the risks. Certainly ensuring that the psychometric analysis and related decisions about the content, scoring, and responsiveness of the new PRO measure is masked to treatment helps to minimize these risks. The organization of an independent psychometric evaluation committee with established standards and methods may provide further assurances that decisions regarding the PRO measure are made separate from bias related to treatment. PRO endpoints represent important and meaningful assessments for understanding the effectiveness of new treatments. For some medical disorders, PROs are the main approach for evaluating treatment effects, and sponsors and researchers need to ensure that these measures are developed and evaluated to most reliably and validly assess health-related outcomes. ■

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Do Payers Find Value in Innovative Trial Designs?
Perspectives from England and Germany

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Introduction

Randomized controlled trials (RCTs) remain the gold standard for evidence-based medicine, but RCTs can be challenging in small patient sub-populations, especially if there is also biological heterogeneity of the disease. Innovative clinical trials are becoming increasingly important to address the problems associated with conducting RCTs. A number of innovative trial designs have been developed, such as the legacy Pick a Winner approach[1]; umbrella trials[2,3] and basket/bucket trials.[4] These trial designs have benefits for researchers, and possibly patients, but how will payers and health technology assessment (HTA) bodies view innovative trial designs?

Regulatory bodies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have shown themselves willing and able to accept innovative clinical trial designs for product registration. However, payers and HTA bodies tend to be fairly conservative in their approach and proscriptive about the evidence that they require.

We looked at the Pick a Winner clinical trial design in more detail and investigated how HTA bodies would react to the inclusion of a clinical trial based on this design in an HTA submission. To gain some further insight into the Pick a Winner clinical trial design, we interviewed Professor Alan Burnett, who designed and implemented – through the United Kingdom Medical Research Council (UK MRC) - the Pick a Winner clinical trial design for clinical trials in acute myeloid leukaemia (AML), and Professor Georg Hess, an innovator and clinical trial expert who has practical experience with these types of designs, as well as being the co-chair of the Early Trial Network (ETN) cooperative group in Germany. We also interviewed Dr. Paul Miller, a health economist and former member of the National Institute for Health and Care Excellence (NICE) Technology Appraisal Committee, and Professor Yvonne Boehler, Vice Dean for Science and Knowledge Transfer at TH Köln, Faculty of Applied Natural Sciences and former Scientific Officer at IQWiG, to understand how HTA bodies would view the Pick a Winner design.

What is the Pick a Winner clinical trial design?

The Pick a Winner design allows multiple treatments to be compared to a standard of care, with rapid removal of ineffective treatments during the trial. Patients are randomized between a control arm and multiple novel treatments. Interim analyses occur after 50 and then 100 patients have been recruited. Treatments that fail to reach a pre-determined level of clinical improvement

are stopped after the interim analysis. The remaining treatment(s) continue to full recruitment and full analysis.

An important part of the design is that there must be the ability to conduct a rapid assessment of outcomes /surrogate outcomes against a standard of care and relatively large minimal clinically relevant difference. This allows the interim analysis to quickly detect which treatments are failing to meet the desired level of clinical improvement. The AML Pick a Winner trial was looking for a doubling of the level of complete response at the interim analysis as the pre-determined level of clinical improvement.

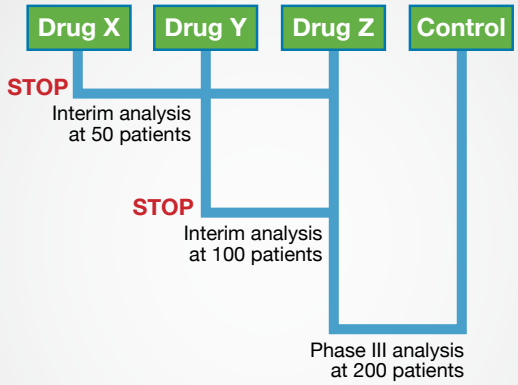
Professor Burnett said that the Pick a Winner trial allows researchers to use fewer patients, particularly in the control arm. This is important in clinical trials for conditions such as AML where outcomes are generally poor, with a median survival of only two to three months, and there are relatively low numbers of AML patients. The trial is able to include a number of medicines at the start of the trial and to add additional medicines through a simple clinical trial protocol amendment.

The Pick a Winner trial design was considered by the FDA and their response was positive suggesting that the design would be suitable for approval. However, it has not yet been formally presented to the FDA as part of an application.

Professor Hess saw that the main advantage of the Pick a Winner design is to show if a drug is promising or not but it is not primarily aimed for approval of a new treatment.

Pick a Winner Design Comparing 3 Drugs

Design included improvements in CR required to progress at each interim analysis (Δ1 at 50 patients and Δ2 at 100 patients)



Drug X fails to Δ1 improvement at first interim analysis
Drug Y fails to show Δ2 improvement at second interim analysis
Drug Z shows Δ1 & Δ2 improvements proceeding to final analysis

CR = Complete Response
Δ1 = change seen at the first interim analysis
Δ2 = change seen at the second interim analysis

How do HTA bodies view innovative clinical trial designs in general?

According to Miller, HTA bodies simply want to make evidence-based decisions. The prime concern of the HTA bodies is that the evidence must characterize the treatment effect and the magnitude of difference compared with the treatment comparator. The gold standard is RCTs, which are preferred by HTA bodies. However, there are issues with RCTs in certain circumstances such as when there is a lack of definition of the standard of care or where researchers are struggling with patient numbers.

Boehler believes that HTA bodies are open to thinking about trial designs which overcome these problems without introducing uncertainties, but they tend not to take a proactive approach, making final decisions about particular clinical trial designs mainly when they receive a submission. This introduces risk for companies submitting data based on innovative clinical trial designs as there may be limited experience in the HTA body in assessing such trials, and therefore an uncertain outcome.

She suggested that there needs to be a forum for discussing innovative clinical trial designs outside of a formal submission. This could include an evidence-based medicine conference such as the Cochrane conference, an internal HTA body dialogue session, or in the context of early scientific advice from the HTA body. This separates the discussion from a formal submission and would allow wider discussion to take place.

What would HTA bodies think about the Pick a Winner design?

Both Miller and Boehler said that the Pick a Winner design was innovative and well thought through. Miller noted that it fits with the current policy drive to allow faster access to new medicines.

However, there were concerns about the potential for bias in the design. This was mainly focused on the control arm being used for each treatment. It is likely that different treatment arms would have different randomization criteria and this needed to be reflected in the control arm being used as the comparison. If the trial continued for several years, there was also the potential for the standard of care to change over time. If patients in the control arm were not contemporaneously recruited, the trial could be comparing patients receiving a novel treatment with an outdated standard of care.

We raised this with Professor Burnett who recognized this potential for bias and had taken this into account in the AML trial that he conducted. In this trial, the randomization of the control arm analyzed was designed to mirror the randomization criteria of the successful

treatment arm. They also only used control patients who were contemporaneously recruited with the successful treatment arm.

Miller was dubious that manufacturers would want to take part in a Pick a Winner trial because of the associated risks and the need to cooperate with competitors. They would certainly not want their treatment to be one of the treatments eliminated in the interim analysis. He saw this type of clinical trial design being more relevant in academic research. Companies may be more interested if their treatment was the winner but are unlikely to want to take the risk.

Suggested Recommendations Regarding Innovative Clinical Trial Designs

Recommendations made by	RECOMMENDATIONS
Payers	• Critically appraise the risk of bias introduced by innovative trial designs, especially with regard to the central HTA-question: Is this drug better than the appropriate comparator treatment? • Seek opportunities to discuss innovative trial designs with HTA bodies besides dossier submissions and be a driver of open, methodological dialogue.
Authors	• Investigate how new trial designs could provide better clinical value substantiation and be used fluidly across indications and stages of diseases in an environment with increasing treatment alternatives. • Increase collaboration between academia, HTA bodies, regulators, and manufacturers to define value substantiation that meets new treatment approaches.

Note: These suggested recommendations represent the thoughts of the authors and those experts interviewed for this article.

Conclusions

We are seeing innovative clinical trial designs being developed and implemented, especially with increasing patient segmentation, personalized medicine, and the advent of the EMA's adaptive pathways, along with the global push for earlier drug approval. Researchers are experimenting with clinical trial design and we can expect to see more alternatives to traditional designs in the future. Some of these designs, like Pick a Winner, will only apply to a limited number of conditions, but others may have wider application and companies need to know how they will be received by payers as well as regulators. As we have mentioned, regulators have been more open to innovative trial designs, while payers have a clear preference for well-designed randomized clinical trials.

Payers and HTA bodies need to watch these developments and consider how they would assess new clinical trial designs. NICE commissioned research to explore the assessment and appraisal of regenerative medicines and cell therapy products[5], raising some methodological issues,[6] but acting as guidance to companies developing treatments in these areas. Similar research and discussions on innovative clinical trial designs would be helpful. ■

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Understanding Payer Sensitivities when Considering the Use of Surrogate Endpoints to Substantiate Clinical Value Propositions

Country Differences between England, Germany, and the U.S.

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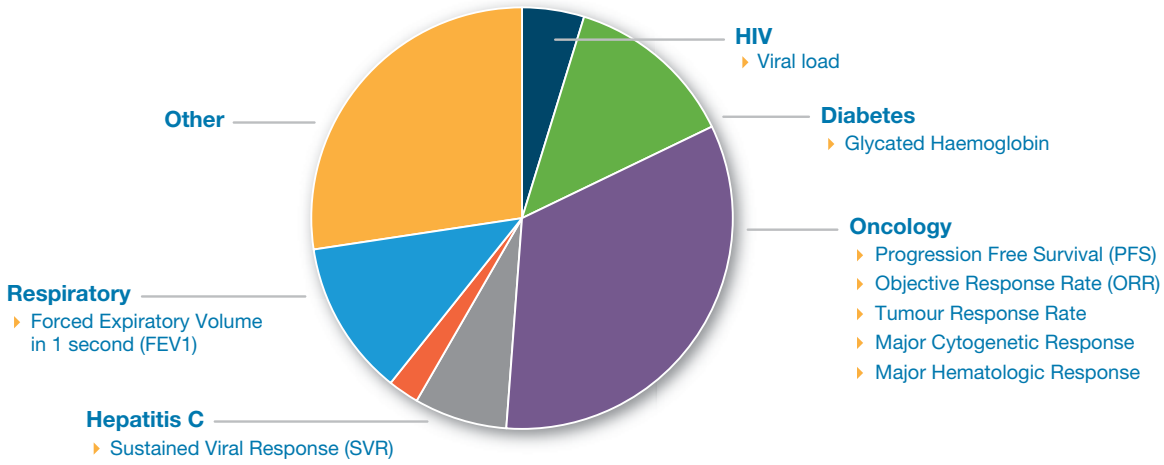
A surrogate endpoint can be defined as an indicator variable substituting for a clinically meaningful endpoint that reflects how a patient feels, functions, or survives.[1] This can include behavioural or cognitive scores, physiologic variables that are indicators of normal biological or pathogenic processes, pharmacological responses to therapeutic intervention, and biomarkers. Changes induced by a therapy on a surrogate endpoint are expected to reflect changes in a clinically meaningful endpoint.[2]

The use of surrogate endpoints in payer and health technology assessment (HTA) evaluations has consistently sparked controversies. Although in many cases a clinical study with a primary surrogate endpoint may be sufficient to achieve regulatory approval, this may be challenged by payers and HTA agencies due to uncertain correlation with a clinically meaningful endpoint. The expectations from payers and HTA agencies as to when a surrogate endpoint is acceptable and specific requirements to ensure validity for decision making can vary considerably across markets, creating clear challenges for manufacturers.

In 2016, the Evidera Market Access Strategy team undertook an investigation on the impact of surrogate endpoints in pricing and reimbursement decision making

Almost half of all novel therapies approved by the U.S. Food and Drug Administration (FDA) in the past five years have relied on surrogate endpoints for demonstration of patient benefit.[3,4]

Graphic 1. Review of Key Therapy Areas within FDA Approvals with Surrogate Endpoints

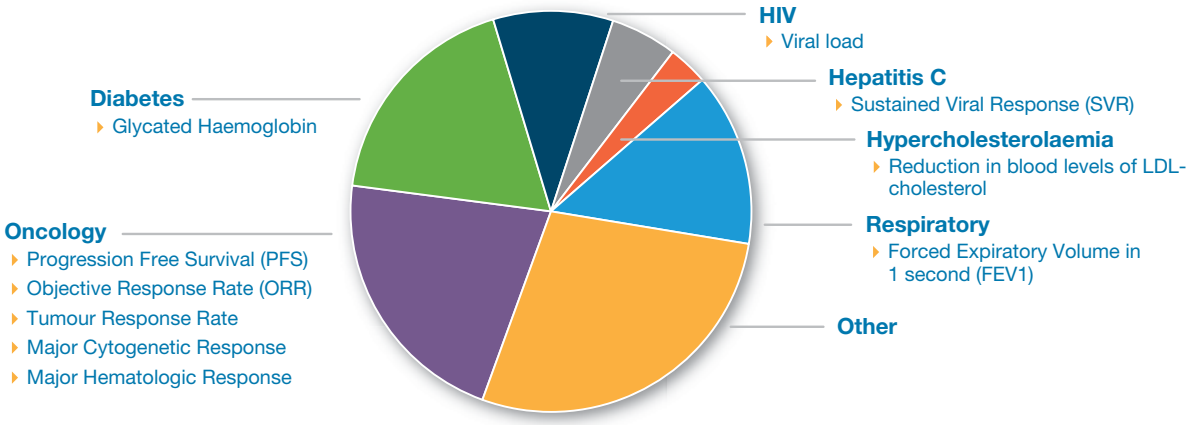


From 2014-2014, 84 of 197 new therapies approved by the FDA relied upon a surrogate endpoint as the primary measure of patient benefit.

Of the 84 therapies approved, 36 had FDA accelerated approvals.[3,4]

Surrogate endpoints have been widely accepted by the European Medicines Agency (EMA) for the regulatory approval of novel therapies.[5]

Graphic 2. Review of Key Therapy Areas within EMA Approvals with Surrogate Endpoints



From 2013-2015, 93 of 244 (around 40%) novel therapies approved by EMA included a surrogate outcome as the primary endpoint within the pivotal regulatory study.[5]

Of the 93 therapies approved, 22 had an EMA orphan drug designation.

with payers in the U.S., England, and Germany. The aim of the research was to identify payer perceptions on the use of surrogate endpoints, differences in acceptability across specific surrogate markers and indications, and expectations for ensuring the validation of a surrogate marker as a patient-relevant measure of therapeutic effect.

At the regulatory level, the FDA and EMA have issued guidance on how to define a surrogate endpoint.

At the payer level, payers consistently highlight that ideally the surrogate endpoint should have a close correlation with hard clinical outcomes to inform decision making. However, in practice, significant variability exists regarding the level of information that payers want to see when assessing surrogate endpoints in pricing and reimbursement evaluations.

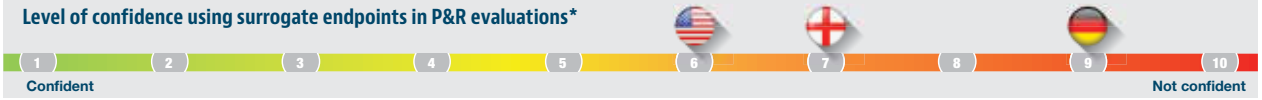
Payers across the U.S. England, and Germany identify important challenges regarding the use of surrogate endpoints as a measure of clinical effect.

Payers across all three markets identify a need for the validation of surrogate endpoints (in terms of the relationship with hard clinical outcomes) and support

Graphic 3.

Country specific payer quotations	What payers want to see when using a surrogate endpoint in P&R evaluations
"Traditionally, the biggest emphasis on surrogates has been in oncology. The issue is always that there are not enough patients and not enough time to have one of the patient-centered endpoints such as overall survival and QoL. These endpoints are what patients are most interested in" – Medical director at large health plan	• Correlation of the surrogate endpoint to a patient centered outcome, e.g., survival, functionality, pain reduction • Strong emphasis on patients' perspective to inform clinical relevance
"I am concerned because I think they have been used as a short cut to achieving regulatory approval and market access in situations where clinical data collection is feasible and necessary to understand the full incremental clinical value/detriments vs. current standard of care" – Former NICE technology appraisal committee member	**NICE will look to the following factors to inform clinical relevance of a surrogate:** • Evidence of correlation to the final clinical endpoint (e.g. validation studies) • Evidence of other markers 'that point in the same direction as the surrogate' • Reported patient relevance of the surrogate endpoint (e.g. from patient organisations)
"It's about whether the endpoint is patient relevant or not. When something is patient relevant then it can be a surrogate endpoint. I am concerned about the inappropriate use of surrogate endpoints (ethically there must be a clear reason not to collect hard clinical endpoints)" – Head of Quality Assurance & drug reimbursement for regional KV	• IQWiG/GBA will require a surrogate endpoint to be validated within a full validation study (i.e. collection of the surrogate endpoint and a hard clinical endpoint within the same study, and comparison of the correlation) • *"The GBA tends to accept surrogate endpoints when there is a clear established relationship to the hard clinical patient relevant endpoint….where the validation trial can be referred to"* – Head of drugs department in sickness fund

Level of confidence using surrogate endpoints in P&R evaluations*



SE: Surrogate endpoints **QoL**: Quality of life **QALY**: Quality-adjusted life years **P&R**: Pricing and Reimbursement

* Based on Evidera study with 6 national payers per market 2016

Graphic 4.

Indication	Surrogate endpoint	Surrogate for	Acceptance in payer assessment	Key findings on payer perception
Hypercholesterolaemia	Level of LDLC	Coronary heart disease, cardiovascular (CV) risk		Payers recognize that "different methods of lowering LDL cholesterol have different clinical outcomes" and many plans are not covering PCSK9 inhibitors because of this. Other plans are restricting use within the labelled indication and awaiting further data on hard clinical endpoints to inform decision making
				Widely considered to be poorly correlated with cardiovascular risk. NICE review of PCSK9 inhibitors resulted in patient access schemes (PAS) and restriction to patients who are not adequately managed with current standard of care (SoC)
				Not acceptable for payers; very low perceived correlation with patient morbidity
HCV	Sustained Virological Response (SVR)	Survival, liver transplant		Widely accepted as a surrogate endpoint for survival, and "about as close as you are going to get to a clinically relevant endpoint". The only information not available is "downstream impact on liver function recovery and whether you are still at risk of cirrhosis"
				SVR 12 and SVR 24 are acceptable endpoints; valued as a surrogate for survival and as a driver of reduced transmission rates
				SVR cannot be equated with "cure" (as this is not validated as a surrogate outcome in line with IQWiG criteria), however SVR is accepted as a surrogate for reduced incidence of liver cancer

Key: Acceptability of surrogate endpoints in P&R assessment

HIGH LOW MEDIUM

* Based on Evidera study with 6 national payers per market 2015/2016

managing the increase in uncertainty within the decision making process. The three key challenges reported on the use of surrogate endpoints are as follows.

1. **Considered as an industry shortcut within clinical development programs**

- Can be seen as a route to rapid regulatory approval without consideration of the actual value/limitations of the surrogate endpoint for communicating the incremental clinical value vs. existing therapies within payer assessment
- Need for an evidence development strategy understanding the advantages and disadvantages of a surrogate endpoint to evaluate the need for additional data generation

2. **Correlation of the surrogate endpoint to the final clinical endpoint**

- A gap between the surrogate endpoint and the final clinical endpoint will create additional uncertainty for decision makers
- Payers request support from manufacturers to understand and manage this additional uncertainty within pricing and market access decision making

3. **Ensuring patient relevance and validation**

- Creating the supporting rationale for the relevance and validity of a surrogate endpoint (in terms of what this practically means for how the patient feels, functions, or survives) often does not receive sufficient time or resources within a product development program

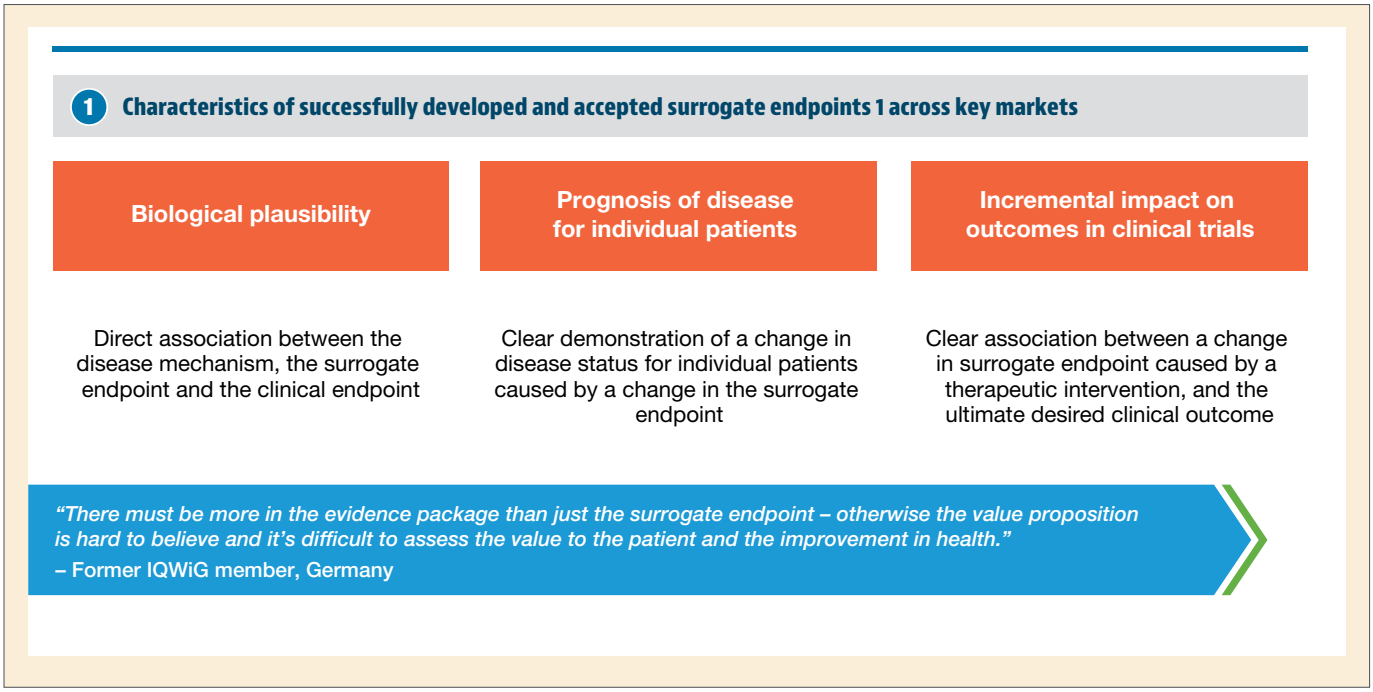
Our research demonstrates varying perceptions of payers across markets on the acceptability of specific surrogate endpoints within decision making and implications for pricing and reimbursement. *(Graphic 4)*

For example, payers across markets accept sustained virologic response as a valid surrogate for patient relevant outcomes in Hepatitis C, however, low density lipoprotein is consistently challenged as a poor surrogate for cardiovascular outcomes/morbidity in the treatment of hypercholesterolaemia.

Conclusion

Despite differences between markets regarding the perception of surrogate endpoints, consistencies are evident in the characteristics of successfully developed and accepted surrogate endpoints. A clear chain of evidence linking a change in the surrogate parameter with a change in clinical outcomes, along with a rationale for the reliance on a surrogate endpoint for demonstrating the clinical benefit of a new therapy, are of key importance to ensure payer acceptance. ■

Graphic 5.



Graphic 6.

Payers require a clear rationale for the reliance on a surrogate endpoint for demonstrating the clinical benefit of a new therapy

2 When to rely on a surrogate endpoint?

✓ **A clear and transparent rationale as to why it is not feasible to collect hard clinical endpoint data**

- E.g., requirement for a long follow-up that is not feasible within a clinical development program (especially important for innovative drugs where there are few alternatives, therefore there may be more pressure to make the drug available)

✓ **All criteria for the validity of a surrogate endpoint are met**

- Consistency of the association between the surrogate and clinical endpoint
- Consistency of the association between surrogate endpoints and patient-important outcomes (e.g., QoL, pain reduction, activities of daily living)
- Evidence from trials in the same drug class that improvement in the surrogate endpoint has consistently led to improvement in the target outcome
- Evidence from trials in other drug classes that improvement in the surrogate endpoint has consistently led to improvement in patient-important outcomes

"When thinking about using a surrogate, my advice is don't take shortcuts, and if there is a feasible way of collecting hard endpoint data, do this, otherwise have a justifiable reason for why you didn't do this or expect payers to penalise you."
– Former NICE Appraisal Committee member

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EMA-HTA Parallel Scientific Advice

Early Dialogue to Support Marketing Authorization and Market Access

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Drug development is a multi-year and cost-intensive process in which marketing authorization is not the final step on the route to optimal market access. Maximum market availability of medical products to patients depends on pricing and reimbursement assessments and agreements made during the health technology assessment (HTA) process, which can take anywhere from six months to more than a year. Recognizing that there are two sets of standards being considered for drug market access, in 2010 the European Medicines Agency (EMA) launched a parallel scientific advice program in which sponsors can obtain input on value decisions from the EMA as well as various HTA bodies. The scheme was permanently implemented after the pilot ended in May 2015 due to the success of the program.

The EMA or the national regulatory agencies, depending on the marketing authorization procedure, determine whether the evidence provided supports a positive risk-benefit balance and warrants the granting of a marketing authorization. Any product approved by the EMA in the centralized procedure will automatically hold a marketing authorization in all the European Economic Area (EEA) member states. Regulators evaluate the evidence generated during the rigorously controlled product development for conformity with applicable scientific, therapeutic, and product specific guidelines. Products need to meet the regulators' expectations for internal validity, quality, safety, and efficacy, while having a positive benefit-to-risk ratio for patient outcomes. Additional evaluation criteria include the impact on the quality of life, the degree of innovation, and whether the medicinal product addresses an unmet medical need. Ideally, new medicinal products should elevate the benefits over existing therapies.

National Health Technology Assessment Bodies (HTAs, including, for example, third-party payers, patient and public representation, pricing and reimbursement agencies) evaluate the value and patient benefit of the approved drug to grant access to health systems at a certain price. Almost all products approved centrally by the EMA will be evaluated by national or regional HTAs following the country's requirements and policies. Some of the criteria used during the marketing authorization stage are considered during the evaluation of the value proposition against evidence requirements and criteria for what constitutes value. HTAs will consider the patient benefit, and selected markets consider cost-effectiveness and/or budget impact of a new medicine. Particularly

with the high price tag of some of the newest, most innovative medicines (e.g., newer antibodies, advanced therapies), affordability influences the decision of making a drug available and setting the specifications for use in the healthcare system. The HTAs may also be responsible for the price, subsequent price renegotiations, and price erosion in the case of real-world effectiveness data.

Sponsors of new medicinal products have to meet the criteria from regulators and HTAs in order to be able to make the product available to patients in a particular market. Swift market availability is supported by the generation of both sets of evidence - in parallel when possible and sometimes consecutively - required for positive decisions as early as possible during the drug development process. The regulatory evaluation is supported by guidelines issued by the regulators. The HTA evaluation is based on guidance and criteria for demonstrating clinical benefit, and where applicable social benefit, and economic benefit.

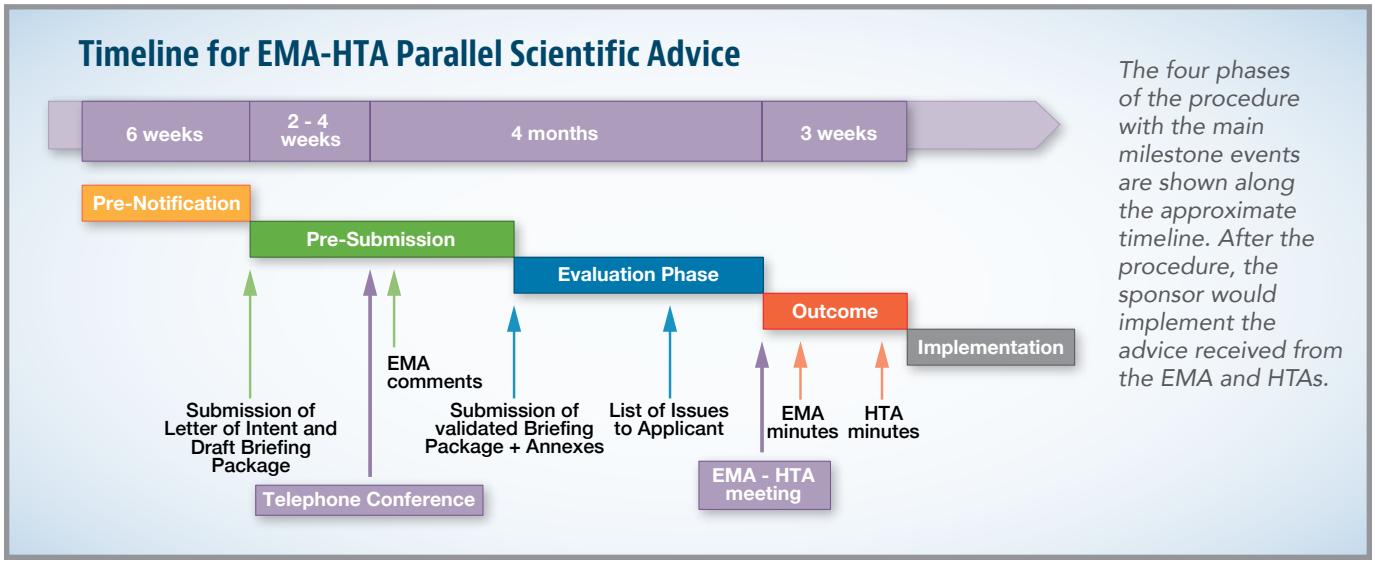
Several initiatives between the EMA and HTAs led up to the implementation of the EMA-HTA parallel scientific advice.[1] The initial focus sought to improve the alignment of information handling and included the assessment of how European Public Assessment Reports (EPARs) provide benefit and risk of medicines by the European High Level Pharmaceutical Forum. Recommendations to improve the HTA effectiveness evaluation were published in a 2008 report.[2] Directive 2011/24 (article 15) also allowed the European Commission (EC) to establish the HTA network (comprised of all member states plus Norway and Iceland) calling for stronger interaction between the EMA and HTAs, timely exchange of information to form stronger synergies, and interactions for all stakeholders.[3] In 2010, the EMA, in collaboration with HTAs, started the pilot program offering parallel advice on evidence requirements for either organization to support market authorization and reimbursement/ pricing decisions. Four EMA-HTA parallel advice procedures were conducted under the Shaping European Early Dialogue for health technologies (SEED) umbrella. The EC-funded SEED project involved a number of HTAs to explore various ways for collaborative early dialogue.

During the EMA-HTA parallel advice meetings, stakeholders can learn about the common and divergent requirements of the agencies involved, to drive a more efficient evidence collection during the development stage.

The EMA-HTA parallel scientific advice procedure follows a four-step process.[4,5] *(Figure 1)*

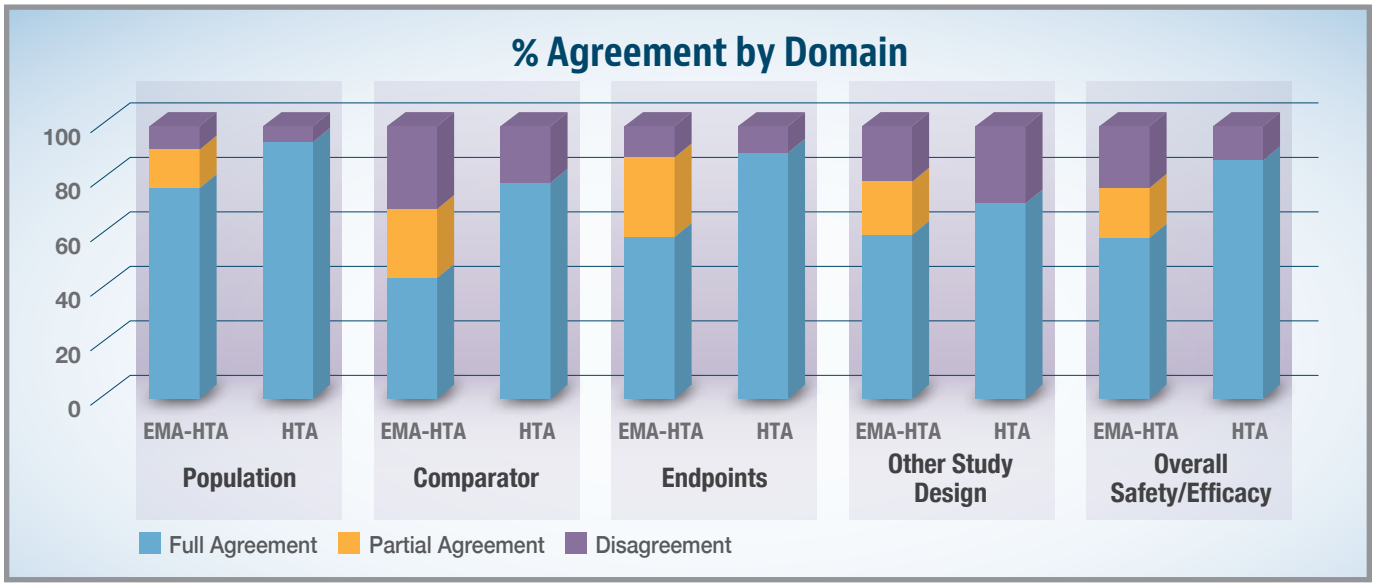
- **Pre-Notification:** The pre-notification phase starts about six months prior to the intended meeting. During this phase the sponsor engages with the EMA and the chosen HTAs for confirmation of the meeting date, preliminary planning of the type of questions to be asked, and whether a pre-submission teleconference is needed. However, the individual HTAs will decide whether to participate in the parallel scientific advice procedure. The pre-notification phase lasts about six weeks.
- **Pre-Submission:** Submission of the letter of intent and draft briefing document to the EMA and applicable HTAs signals the start of the pre-submission phase. The pre-submission phase lasts about three weeks if the sponsor does not request a teleconference or about seven weeks if a teleconference is requested. A pre-submission teleconference generally is recommended for more complex and/or controversial

Figure 1. Timeline for EMA-HTA Parallel Scientific Advice



The four phases of the procedure with the main milestone events are shown along the approximate timeline. After the procedure, the sponsor would implement the advice received from the EMA and HTAs.

Figure 2. Degree of Agreement between the EMA and HTAs



The agreement in responses to questions was analyzed by domains and evaluated by agreement between the EMA and HTAs (EMA-HTA bars) or among HTAs (HTA bar).

programs. It allows for a discussion of the scope of advice and the appropriateness of the preliminary questions. Any comments on the briefing package following the pre-submission conference will be sent to the sponsor in writing by the EMA. The applicant will then send the final, revised briefing document with all annexes for EMA and HTA validation.

- **Evaluation Phase:** Once the briefing package has been validated, the applicant sends it to the EMA and all applicable HTAs via EudraLink. The submission of the briefing package marks day one of the scientific advice procedure. The EMA and HTAs evaluate the briefing package independently and may send lists of issues to facilitate the discussion. The evaluation phase culminates in a face-to-face meeting to discuss the questions and provide the appropriate feedback on available and further required evidence for positive outcomes in a future marketing or pricing/reimbursement application evaluation.

- **Outcome:** The EMA and HTAs will provide their advice independently. The EMA will provide written meeting minutes within five working days, whereas the HTAs provide their responses within 15 working days in their individually preferred format.

The advice provided by the EMA and HTAs is non-binding.

During the procedure, the sponsor can direct questions to the EMA and HTAs or only to the EMA or the HTAs. Regional and national regulations, as well as other factors, will influence the responses of the HTAs and/or the involvement of further relevant advisory bodies.

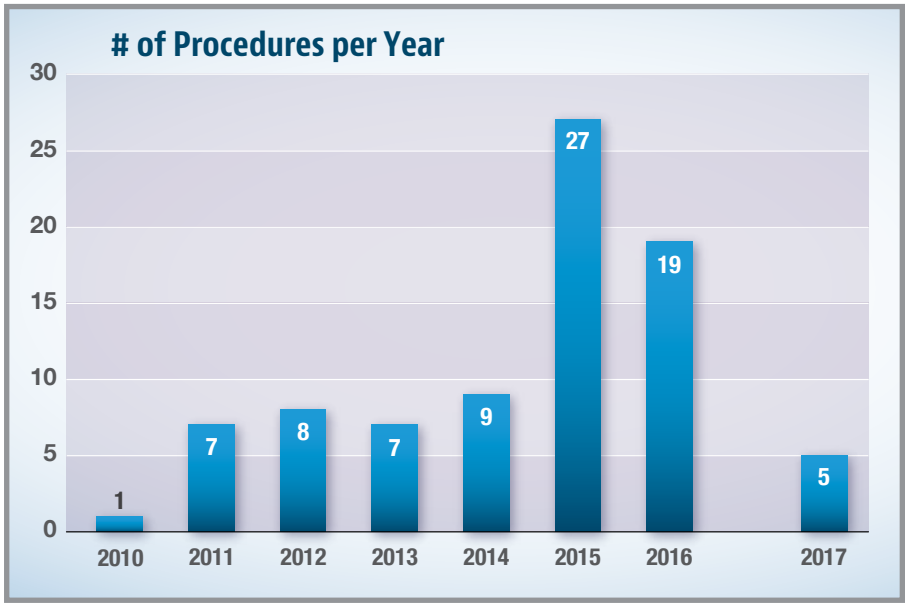
Tafuri, et al.[6] conducted an analysis of the agreement level for 31 EMA-HTA parallel scientific advice procedures conducted between the launch in 2010 and 1 May 2015 (cutoff date for the evaluation of the pilot).[6] The procedures were analyzed based on the meeting minutes and only included those where the evaluation of agreement between EMA and HTA advice was directly possible. A total of 375 questions with 588 answers from HTAs were evaluated for their agreement with the EMA. Some 70 answers were not 'assessable', leaving a total of 518 answers for evaluation. The majority, 61% (317 of 518), were regarded as full agreements, while disagreements only accounted for 16% of the answers (83/518 – *Figure 2*).

The analysis further groups the questions into domains: population, comparator, endpoints, other study designs, etc. The population domain includes questions regarding the inclusion/exclusion criteria, therapeutic indication, biomarkers/subgroups, and extrapolations, while the endpoint domain includes considerations regarding primary efficacy endpoints, patient-related outcomes, health-related quality of life secondary endpoints, and clinical relevance to effect size. Other study design considerations include randomization, treatment duration, dosing, and analysis methods. Tafuri, et al.[6] and the EMA's Report[1] find the highest level of agreement for the population domain with 77% in full agreement and 14% in partial agreement. The lowest level of agreement - 44% in full agreement and 25% in partial agreement

- was found for comparator-related questions. The agreement level in other domains ranged between the population and comparator domains. On the other hand, the HTAs agreed among themselves in 94% of cases for the population domain and 90% for the endpoints. The lowest agreement among HTAs was for other study designs (71%) and again the comparator domain (74%). The agreement level for the remaining domains was in the high 80%.

Since the start of the initial pilot in 2010 and up to March 2017, 92 EMA-HTA parallel scientific advice procedures were conducted (*Figure 3*).[1,7]

Figure 3. Number of EMA-HTA Parallel Scientific Advice Per Year



Although the initial years saw a limited number of procedures conducted, the number of EMA-HTA parallel scientific advice procedures significantly increased in recent years. Five procedures were conducted up to March 2017.

Of the 63 procedures conducted (59 non-SEED and 4 SEED) between 2010 and 31 December 2015, 38% addressed antineoplastic immunomodulating drugs, 13% the nervous system, and 11% were general anti-infectives for systemic use. The remaining therapeutic areas generally accounted for less than 10% of the total procedures. The majority of procedures (31) were conducted for chemical entities (49%), with 27 products (47%) being bio (technology) derived and 5 (8%) being advanced therapies. Patient representatives participated in 40% of the procedures with almost 60% of those (17) stemming from 2015, after the routine invitation of patient representatives was initiated in December 2014.[1]

The National Institute for Healthcare and Excellence (NICE) from the United Kingdom (86%), the Federal Joint Committee (Gemeinsamer Bundesausschuss - G-BA) from Germany (66%), and the Agenzia Italiana del Farmaco (AIFA) from Italy (37%) participated in the most of the 59 parallel advice procedures conducted by the end of 2015.[1] On average, three HTAs (range 1–5) participated per scientific advice procedure.

Of the participating HTAs, NICE was by far the most frequent participant, perhaps at least in part based on their long-standing experience in providing scientific advice to inform sponsors from the value-driven perspective used by HTAs to determine market access. NICE started providing single country scientific advice in 2009.[8] By the end of 2015, NICE had completed 166 scientific advice procedures, including NICE-only scientific advice and single-country Medicines and Healthcare Products Regulatory Agency (MHRA)-NICE scientific advice, and contributed to multi-country scientific advice under the EMA-HTA pilot program. Of the 166 scientific advice procedures conducted by NICE, 146 products remained at the development stage or failed during development. Of the remaining products, 16 products were authorized; one was pending authorization at the time of analysis, and three did not gain a marketing authorization. Of the 16 authorized products, 12 products underwent the post-marketing authorization NICE technology appraisal and nine received a positive opinion. Two evaluations are still ongoing, and for one, NICE could not make a determination since the manufacturer did not submit any materials.

Although it is impossible at this stage to draw conclusions about the success rate of receiving market access due to an HTA scientific advice procedure, the data presented for the NICE procedure would suggest a positive correlation. NICE and EMA have noticed an increased interest in the HTA scientific advice procedure and note that the process and interactions will continue to evolve as stakeholders gain insight into each other's requirements and assessment methods. The EMA's early access tools, PRIority MEdicines (PRIME)[9] and Adaptive Pathways[10] (see also *PRIME turns One* article in this issue) recognize the importance of receiving HTA advice at an early stage during drug development to optimize evidence generation to support marketing authorization, as well as market access, through the pricing and reimbursement determination. ■

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PRIME Turns One
PRIME and Other Early Access Tools

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The European Medicines Agency's (EMA) PRIority MEdicines Scheme (PRIME) turned one year old in March 2017.[1] PRIME supports the development of medicines addressing unmet medical needs and medicines that provide a therapeutic advantage over existing treatments. This is achieved by offering the sponsor early, proactive, and enhanced support, which builds on the existing regulatory framework and tools to enable early patient access to innovative medicines.[2] This newest scheme provides some clear advantages over other programs, such as accelerated assessment, conditional marketing approval, and compassionate use, and can be used in conjunction with these programs. Other initiatives such as Adaptive Pathways and EMA-HTA (Health Technology Assessment) Parallel Scientific Advice also support clinical program development geared toward early patient access to innovative medicines.

"PRIME fosters the efficient development of medicines by reinforcing scientific and regulatory advice provided at various stages of the development program, and enhances communication between the sponsor and the EMA through the assigned contact points."

PRIME was originally proposed in a Reflection Paper in 2015 and then launched in March 2016.[3,4] In the first year, the EMA evaluated 91 applications and accepted 19 products into the program with one program discontinuation (five applications were considered to be out of scope).[5] The majority of products (56%) are advanced therapy medicinal products (i.e., tissue-engineered products, gene and cell therapies), with chemical drugs being the second largest group *(Figure 1)*. Although the scheme aims to support academic research groups and small to medium-sized enterprises (SMEs) specifically, only 42% of successful applications stemmed from SMEs with no applications thus far from academic institutions *(Figure 2)*.

To be eligible for PRIME, the proposed treatments generally must meet the eligibility criteria for accelerated assessment, i.e., they are medicinal products of substantial public health interest, particularly from the perspective of therapeutic innovation. A strongly substantiated mechanism of action, supportive preclinical data, and first-in-human (FIH) tolerance data, at a minimum, should be available. However, for candidates from small and medium-sized businesses and academia,

entry prior to the collection of human tolerance data may be possible according to the guidance.[7] However, clinical data at the exploratory stage generally is expected and significantly increases the chances of acceptance. Benefits for eligible sponsors include the following:

- Expected eligibility for accelerated assessment for the marketing authorization application
- Early appointment of a Committee for Medicinal Products for Human Use (CHMP) or Committee for Advanced Therapies (CAT - for Advanced Therapy Medicinal Products [ATMP]) Rapporteur
- Scientific advice on the overall development plan and at key developmental milestones with the involvement of appropriate stakeholders (e.g., regulators, HTA agencies, patients)
- Kickoff meeting to understand the development program and obtain preliminary guidance on the requirements for the marketing authorization application
- Dedicated contact point at the EMA

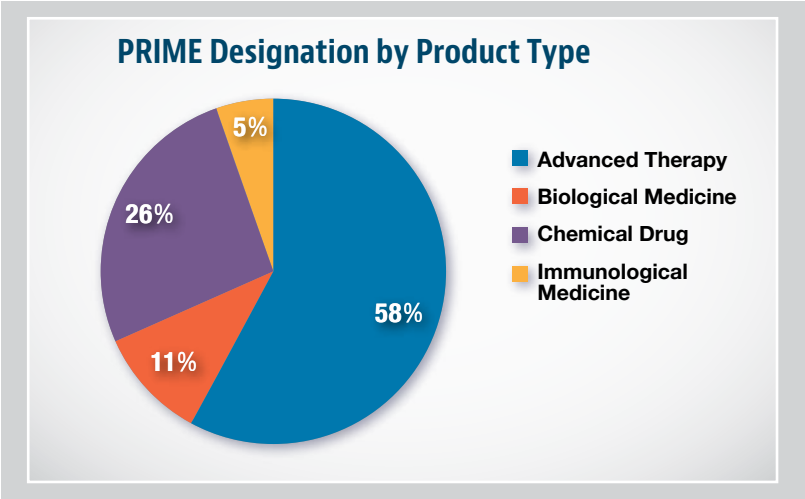
Some benefits will be delayed for sponsors entering with very limited or no clinical data. Only one of the 19 PRIME designated products provided only nonclinical and tolerability FIH data: A4250, a selective inhibitor of the ileal bile acid transporter for the treatment of progressive familial intrahepatic cholestasis by Albireo.[6]

PRIME fosters the efficient development of medicines by reinforcing scientific and regulatory advice provided at various stages of the development program, and enhances communication between the sponsor and the EMA through the assigned contact points. The support and guidance provided allow for an optimized and efficient development program for the generation of robust data supporting marketing authorization. Eligibility for accelerated assessment will be confirmed during the development program and further enabled through the sponsor-agency interactions.

There are several other early access tools for sponsors of medicines addressing unmet medical needs: accelerated assessment,[8] conditional marketing authorization (CMA),[9] and compassionate use[10] at the European Union (EU) level with some supplemental national programs *(Figure 3)*. Generally, programs can be used in combination, e.g., PRIME already rolls accelerated assessment into the advantages of the designation.

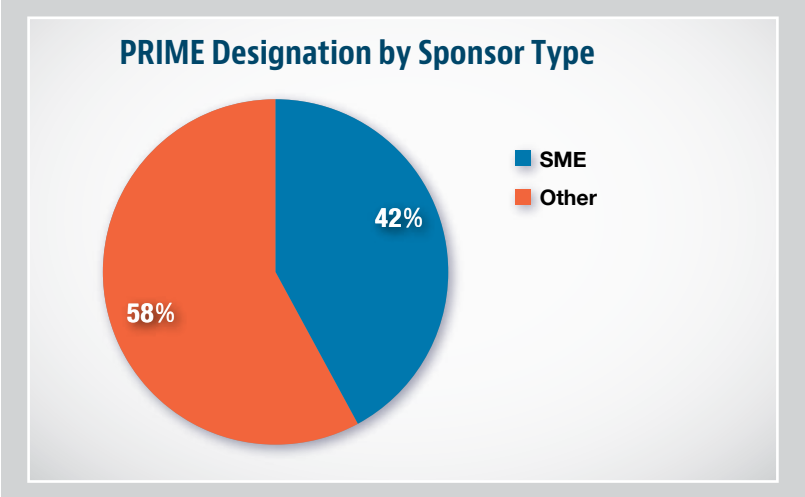
Accelerated assessment reduces the evaluation of a centralized marketing authorization application to 150 days.[8] The standard timeframe could be as much as 210 days depending on clock-stops initiated by requests for further information. Accelerated assessment is, itself, a program facilitating early access to medicines for patients. Sponsors would generally apply at least

Figure 1. PRIME Designation by Product Type



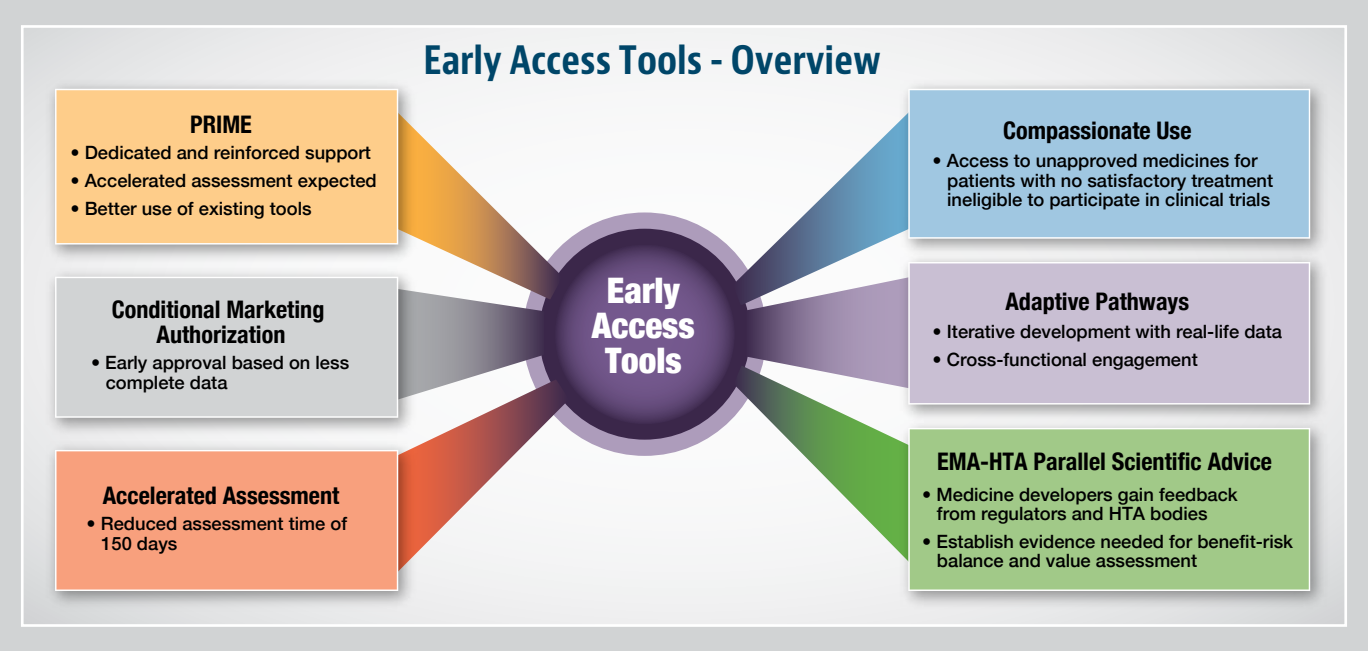
Percent of designations per product type of advanced therapy, biological, chemical, and immunological medicines of the total of 19 granted designations up to 23 March 2017.[6]

Figure 2. PRIME Designation by Sponsor Type



PRIME was implemented to support academic research groups and smaller biotechnology companies in particular; nonetheless, only 42% of the 19 designations were from SME applicants. However, including the declined applications, 46 applications (50%) came from SMEs, including one from an academic institution, and 40 applications (43%) from others.

Figure 3. Early Access Tools



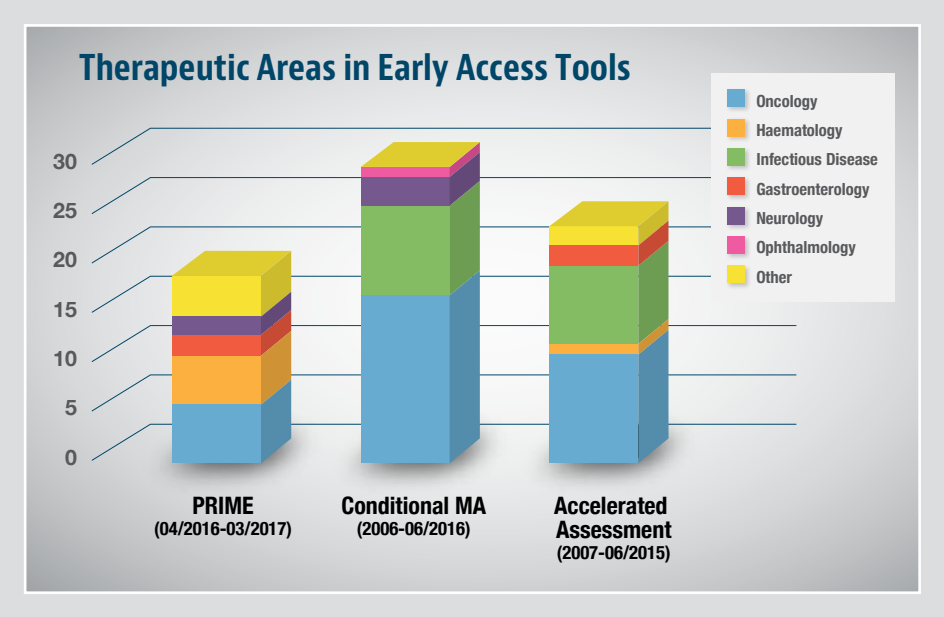
Several early access tools are available within the European Union to support faster patient access to therapies for unmet medical needs in serious and life-threatening diseases.

two to three months before the intended filing date for the marketing authorization to determine eligibility for accelerated assessment. However, the EMA strongly recommends a pre-submission meeting six to seven months in advance of filing to discuss the sponsor's intentions. The justification for eligibility for accelerated assessment must show that the medicinal product is of major health interest and an innovative therapeutic. Products accepted into the PRIME scheme generally are expected to qualify for accelerated assessment.

CMA may be granted for medicines that address an unmet medical need, where the immediate availability to patients outweighs the risk of the less comprehensive data available.[9] To qualify, medicines must belong to at least one of three categories: a) treat, prevent, or diagnose a seriously debilitating or life-threatening disease; b) intended for emergency use; or, c) designated as an orphan medicine. CMA is granted with specific obligations attached that ensure that comprehensive data will be available for the medicine in due course and the conditional approval can be converted into full approval. CMA is valid for one year and can be renewed with the aim to receive full marketing authorization by providing comprehensive data collected by completing the specific obligations.

The EMA published a 10-year report assessing the program from July 2006 to June 2016.[11] During that time, 30 medicines received CMA (6 additional applications received a positive recommendation from CHMP for CMA, but were not yet authorized at the time of data lock for the report and were therefore not included in the overall calculations). The average time to receive full marketing authorization was 4 years (0.48 to 7.12 years). Two-thirds of CMA applications were justified by 'no approved satisfactory treatment' (11) and 'improved treatment effect and/or safety vs. available therapies' (9). Only 14 marketing authorization applications contained the request for CMA consideration in the initial request, which may indicate a certain reluctance by sponsors to apply for this pathway. The consideration of CMA during the review procedure (14) or re-examination (2) generally led to longer review times due to clock-stops. Fifty-eight pivotal studies were identified and 31 of these were Phase II (including Phase I/II and IIb), with 21 pivotal Phase III studies. Almost two-thirds of applications receiving CMA (18) had prior scientific advice or protocol assistance. Eleven of the products converted their CMA to a full marketing authorization, 2 were withdrawn, and the remaining are still CMAs with less than 5 years of authorization. Over the past 10 years, there were only 22 unsuccessful applications for CMA (negative CHMP opinion or withdrawal by sponsor). Although there was a slight uptick in the applications for 2014 and 2015, no clear trend is discernible. Compared to the PRIME designation, very few requests have been received over the past 10 years. The appropriateness of considering a CMA for a PRIME-granted product should be addressed during one of the scientific advice meetings at key development milestones.

Figure 4. Early Access Tool Utilization by Therapeutic Area



Number of applications granted for PRIME,[5] CMA[11] and accelerated assessment[12] for the timeframes, as indicated, as they address different therapeutic areas. There were a total of 19 PRIME designations, 30 CMA, and 24 accelerated assessment applications granted.

Generally, therapeutics for oncology indications made up the majority of products being eligible for an early access tool. Infectious disease products also played a major role for CMA (new chemical entities only) and accelerated assessment. However, none of the seven PRIME applications for a product to treat an infectious disease were successful. The remainder of granted applications were for a variety of therapeutic areas *(Figure 4)*.

Compassionate use is an EU-wide program, which permits unauthorized medicines to become available to groups of patients under very specific and strict conditions. Compassionate use only applies to life-threatening, long-lasting, or seriously debilitating illnesses that cannot be treated with existing authorized medicines. Contrary to other early access programs, the use of a medicine in the compassionate use setting needs to be initiated by the national competent authority wishing to make the medicine available before authorization. Generally, the medicine must be undergoing clinical trials, and the EMA will offer an opinion on compassionate use. Currently, only four products have an opinion on their use under the program: Ledipasvir/Sofosbuvir, Daclatasvir, Sofosbuvir Gilead, and IV Zanamivir.[10] Three of those products are for the treatment of Hepatitis C, with the fourth for life-threatening influenza Virus A or B. Appropriateness of compassionate use should be determined at one of the sponsor meetings with the EMA.

Adaptive Pathways[13] is another of EMA's schemes to accelerate patient access to new innovative medicines. A pilot was initiated in 2014 for two years and 18 proposals were accepted for the initial face-to-face meeting to discuss the pathway. Adaptive Pathways is based on three principles: 1) iterative development including CMA and compassionate use; 2) real-life use to supplement clinical trial data through patient registries and pharmacovigilance; and, 3) early involvement of other stakeholders such as patients and HTA bodies (also see "EMA-HTA Parallel Scientific Advice" article in this issue). The key takeaway points from the pilot include that adaptive pathways can foster a multi-stakeholder communication to: 1) agree on a development program optimizing and aligning requirements as much as possible; 2) provide information for prospective planning of the development program; 3) aim to generate data for a common evidence base to address different stakeholders needs; and, 4) support evidence generation in challenging therapeutic areas.[14] However, the program is not for all products and needs to be carefully evaluated. Also, the involvement of patients, healthcare professionals, and payers in advice procedures needs further optimization. The EMA continues to explore the adaptive pathways approach, particularly in respect to parallel advice from EMA and HTA, and issued guidance for potential applicants.

The United Kingdom (UK) implemented the Early Access to Medicines Scheme (EAMS) in 2014, allowing the availability of promising new unlicensed medicines to treat high unmet medical needs to UK patients without delay.[15] The voluntary scheme follows a two-step evaluation: 1) assessment of clinical data to determine if the medicine would qualify as a Promising and Innovative Medicine (PIM); and, 2) scientific opinion assessing the benefit-risk ratio on the application by the Medicines and Healthcare Products Regulatory Agency (MHRA). Application for the EAMS requires sponsors to engage early with relevant decision bodies, including payers. All EAMS medicines are provided to the National Health Service (NHS) free of charge until a positive funding policy can be reached by the HTA.

PRIME has been likened to the U.S. Breakthrough Therapy Designation (BTD) that has been available as

an early access tool for the past five years.[16] The BTD is designed to expedite the development and review of drugs for serious conditions and life-threatening diseases that show preliminary clinical evidence indicating a substantial improvement on a clinically significant endpoint. Generally, clinically significant endpoints include those that measure an effect on irreversible morbidity or mortality, or symptoms that are serious consequences of the disease. A drug development program that receives BTD status will be eligible for other early access tools including fast-track designation (including priority review), intensive guidance during the development program, and an organizational commitment to involve senior U.S. Food and Drug Administration (FDA) managers. The BTD designation was implemented in July 2012 as part of the FDA Safety and Innovation Act (FDASIA) and guidance was published in May 2014.[17] From the implementation in 2012 through 30 September 2016, the FDA received 392 applications of which 141 designations were granted and 195 denied.[16] Twelve of the PRIME designated products have also publicly disclosed that they received BTD.[18] However, that does not mean that the other seven PRIME products do not qualify for BTD; there may be simple strategic considerations that offset the timing of applications. Both programs attract very similar product categories, while PRIME allows for candidates with less clinical experience and attracts more advance therapies. Additionally, PRIME allows for the early engagement with HTA bodies which ultimately make the market access decisions while the BTD does not engage in these discussions.

Choosing to apply for the PRIME scheme is a viable option for consideration for medicines that address an unmet medical need at an early clinical stage. The scheme provides consistent regulatory support through the assignment of a rapporteur, a dedicated contact point at the EMA to facilitate all interactions and enhanced interactions, including scientific and product development advice from multiple stakeholders, such as payers and/or patients. The scheme aims to optimize evidence collection to allow for faster patient access by including payers and other stakeholders in the clinical development program discussion. Products chosen for PRIME also may benefit from reduced review times through accelerated assessment. Should the EMA decide a potential medicine is not eligible for PRIME, the decision is made without prejudice and only minimal information is published by EMA. The sponsor can reapply once additional supportive clinical information becomes available. Additionally, access to the other early access tools mentioned here is not prevented due to ineligibility for PRIME. Each early access tool addresses a particular facet and the sponsor should consider capitalizing on these other tools. The applications for the PRIME scheme are short (less than 30 pages) and a decision is reached quickly (within 40 days). The benefits of acceptance into the scheme are likely to maximize the use of sponsor resources during clinical research, resulting in cost- and time-efficient drug development for much needed innovative medicines addressing unmet medical need. ■

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The IQWiG Checklist for Indirect Comparison and Network Meta-Analyses

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In times where health technology assessment (HTA) bodies demand increasing amounts of evidence in order to grant reimbursement for a newly developed drug, it has become vital for pharmaceutical companies to find innovative and efficient ways to demonstrate their products' added benefit. While head-to-head comparisons are still preferable in the eyes of Germany's Federal Joint Committee (G-BA), indirect comparisons and network meta-analyses with other existing products can provide a smart way to circumvent setting up additional trials or testing. However, they are riddled with pitfalls that could give reason to disregard the comparison as valid evidence.

Common problems are poor choice of trials included, non-validity of the underlying assumptions, and issues with the applicability/validity of the statistical methodology.

The following list published by the Institute for Quality and Efficiency in Health Care (IQWiG) contains nine questions on central aspects of conducting a network meta-analysis or an indirect comparison. The list does not cover technical details, especially those on statistical methodology, however, it does enable companies to gauge which questions IQWiG might ask when assessing their indirect comparisons or network meta-analyses. Considering these questions before designing an analysis can increase the likelihood of a successful assessment outcome. ■

For more information, please email info@evidera.com.

Assessment of Indirect Comparisons and Network Meta-Analyses

1. Has the question been established a priori?
   - Clear description of the question
   - Transferal into statistical hypotheses
   - Explanation of deviations from the originally established plan
2. Has the rationale for the use of an indirect comparison been explained sufficiently?
3. Has the choice of a common comparator in lieu of a direct comparison been explained sufficiently?
4. Has a systematic and thorough literature review been conducted and has it been described in detail?
   - For the intervention of primary interest?
   - For the common comparator?
5. Have initially defined inclusion and exclusion criteria been used and described?
6. Was there a complete report of all relevant study data?
   - Characteristics of all studies included
   - Assessment of all studies included
   - Graphics of the network, description of network geometrics
   - For all relevant endpoints, comparisons and sub-groups:
     - Individual results of all studies (effect estimates and corresponding confidence intervals)
     - Effect estimates and confidence intervals from paired meta-analyses
7. Have the core assumptions been researched and have the results from this research been treated adequately?
   - Similarity
   - Homogeneity
   - Consistency
8. Have adequate statistical tools been used and have they been described in sufficient detail?
   - Use of adjusted indirect comparisons
   - Treatment of studies with multiple groups
   - Technical details (especially when using Bayesian model)
   - Program code
   - Sensitivity analyses
9. Have limitations been described and discussed sufficiently?
   - Quality and exhaustiveness of the database
   - Methodological uncertainties, sensitivity analysis
   - Conflicts with core assumptions

Checklist provided by IQWiG on indirect comparisons (From: Auf den Punkt gebracht, Zahlen und Fakten aus dem IQWiG 2016; IQWiG January 2017(2)). https://www.iqwig.de/download/2016_IQWiG_Auf_den_Punkt_gebracht.pdf

Are Clinical Guidelines Informed by HTA Decision Making?
A German Analysis by IQWiG

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Clinical guidelines influence clinical decisions on diagnostics and treatments, rules of operation at hospitals and clinics, and in some countries healthcare spending by governments and insurers is also being influenced by guidelines. As defined by the Institute of Medicine, clinical guidelines are "statements that include recommendations, intended to optimize patient care, that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options."[1] They may offer concise instructions on which diagnostic or screening tests to offer, how to provide medical or surgical services, how long patients should stay in the hospital, or other details of clinical practice.

The type of information included in a clinical guideline should come from a systematic review of the available evidence. To most 'market access' savvy audiences it may seem appropriate that information from health technology assessments (HTAs) be included in national clinical guidelines. However, an investigation conducted by the Institute for Quality and Efficiency in Health Care (IQWiG) in 2016 found that information from the Pharmaceuticals Market Reorganisation Act (AMNOG) benefit assessments have not been included in German S3-guidelines to date.[2,3] IQWiG scientists investigated the extent to which AMNOG findings are cited/considered in the German guidelines. As of 2 October 2015, 133 dossier assessments have been conducted. At the same time, there were 141 up-to-date S3, 28 of which focused on indications where AMNOG-assessed medicines are used. Of these 28 guidelines, 12 were updated after the publication of Germany's Federal Joint Committee (G-BA) resolution on related medicines and could potentially include G-BA's findings and recommendations.

Results: Only 3 out of 12 guidelines mentioned the respective AMNOG assessments with none of the 3 presenting the content of AMNOG documents. ■

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German Guideline Information

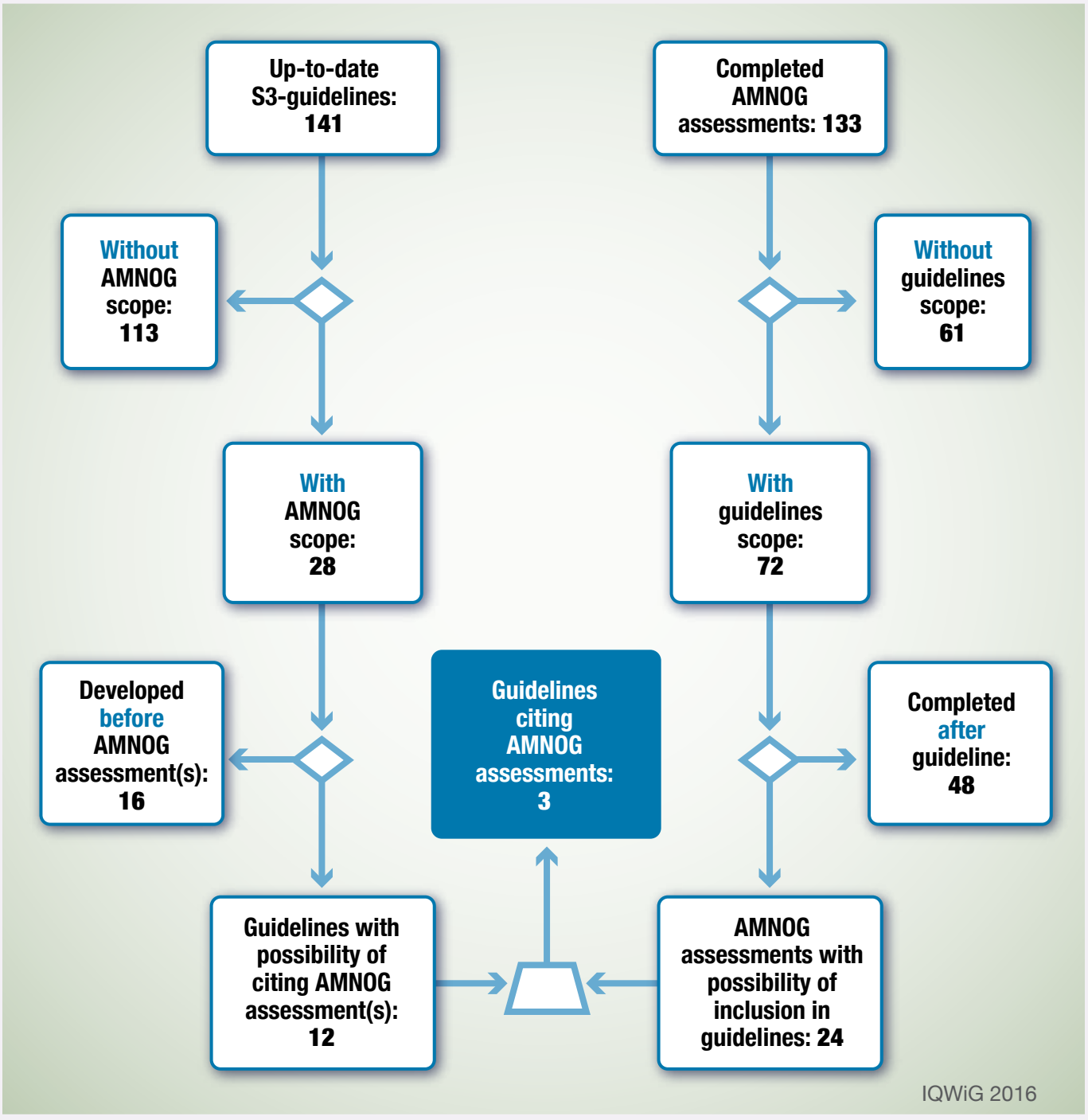
S1: The guideline was developed by an expert group in an informal consensus.

S2k: A formal consensus-finding has taken place.

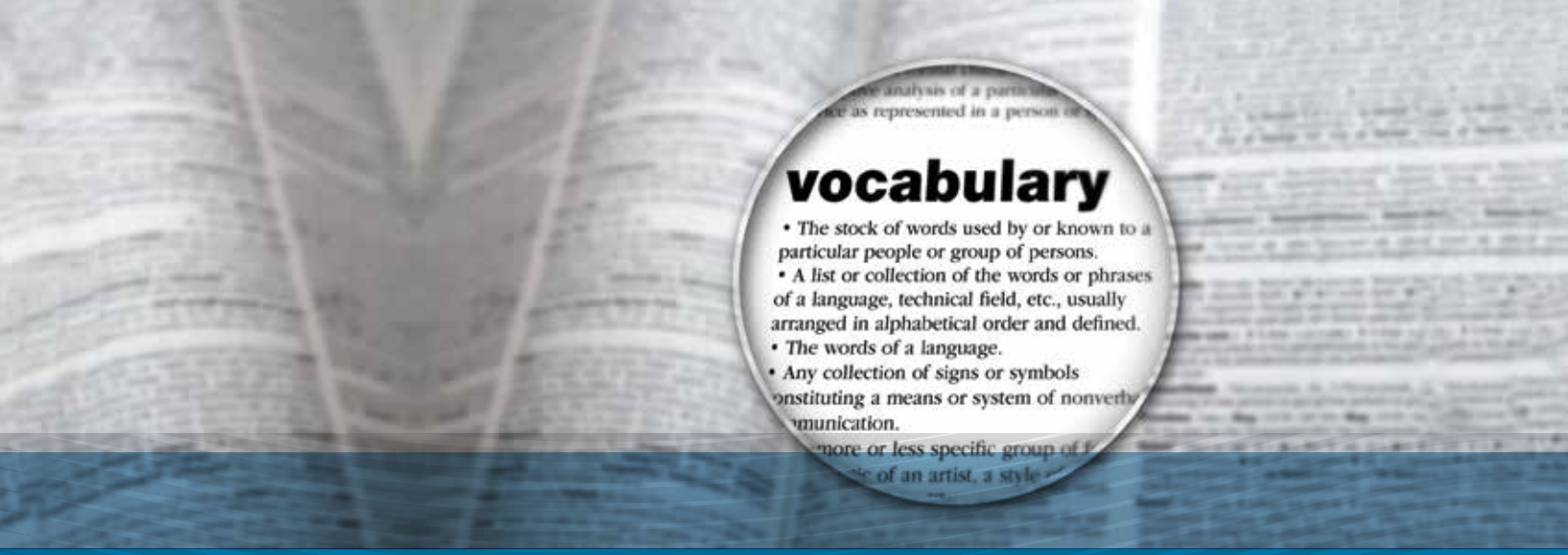
S2e: A systematic evidence research has taken place.

S3: The guideline has gone through all elements of a systematic development (logic, decision-making and outcome analysis, evaluation of the clinical relevance of scientific studies and periodic review).

Citations of AMNOG Assessments in Guidelines are Very Rare



Graphic from *Auf den Punkt gebracht, Zahlen und Fakten aus dem IQWiG 2016*



Clinical Vocabularies for Global RWE Analysis

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Introduction

A significant volume of real-world evidence (RWE) analyses continue to be conducted with data repurposed from healthcare administrative databases. The range of sources represented by those databases has grown in response to demand for richer description of patient health status and outcomes. Data availability, including the range of available data sources, has grown unevenly across the globe in response to country-specific market and regulatory dynamics. Nonetheless, as demand globalizes for RWE insights from databases, those demands increase pressure on analysts to find ways to bridge differences between local data sources to achieve comparable insights across regions.

One of the challenges in bridging differences across databases is the codes used to represent key clinical facts. Historically, RWE database studies have leveraged local code sets for cost-bearing healthcare services such as drugs, procedures, and laboratory tests. While diagnosis codes have long been globalized (the International Classification of Diseases, or ICD, is maintained by the World Health Organization), adoption of specific diagnosis code revisions has occurred inconsistently by country and region.

Two dynamics are increasing pressure to use more globalized codes for the full range of clinical facts in RWE database analyses. One is the increased set of incentives for providers' administrative systems to exchange information for improved quality and coordination of care, often using standardized messaging systems such as Health Level 7 (HL7). These messages are only as good as the standardization of codes between message senders and receivers, which motivates the encoding of facts using common code sets. The second is the increased availability of common data models to standardize the extraction and analysis of these data for RWE and drug safety purposes. While common data models make compromises on the structure of tables and fields extracted from healthcare systems such as electronic medical records (EMR) and billing systems, they can improve consistency and replicability of analyses by mapping data values to globally standardized clinical codes.

Analysts faced with using more clinically rich or globally standardized data will need to master new coding systems. This paper provides a brief primer on several of these global clinical terminologies: LOINC, SNOMED CT, and RxNorm. We'll highlight the origins, structure, content, and overlap of each, and will also highlight novel ways to leverage these global code sets even when they have not been included within a particular database.

Table 1. LOINC Codes Related to "Hemoglobin A1c."

LOINC	LongName	Component	Property	Timing	System	Scale	Method	Units
4548-4	Hemoglobin A1c/ Hemoglobin.total in Blood	Hemoglobin A1c/ Hemoglobin.total	MFr	Pt	Bld	Qn		%
55454-3	Hemoglobin A1c in Blood	Hemoglobin A1c	—	Pt	Bld	—		
41995-2	Hemoglobin A1c [Mass/ volume] in Blood	Hemoglobin A1c	MCnc	Pt	Bld	Qn		g/dL
17855-8	Hemoglobin A1c/ Hemoglobin.total in Blood by calculation	Hemoglobin A1c/ Hemoglobin.total	MFr	Pt	Bld	Qn	Calculated	%
4549-2	Hemoglobin A1c/ Hemoglobin.total in Blood by Electrophoresis	Hemoglobin A1c/ Hemoglobin.total	MFr	Pt	Bld	Qn	Electrophoresis	%
17856-6	Hemoglobin A1c/ Hemoglobin.total in Blood by HPLC	Hemoglobin A1c/ Hemoglobin.total	MFr	Pt	Bld	Qn	HPLC	%
62388-4	Hemoglobin A1c/ Hemoglobin.total in Blood by JDS/JSCC protocol	Hemoglobin A1c/ Hemoglobin.total	MFr	Pt	Bld	Qn	JDS/JSCC	%
71875-9	Hemoglobin A1c/ Hemoglobin.total [Pure mass fraction] in Blood	Hemoglobin A1c/ Hemoglobin.total	MFr.DF	Pt	Bld	Qn		
59261-8	Hemoglobin A1c/ Hemoglobin.total in Blood by IFCC protocol	Hemoglobin A1c/ Hemoglobin.total	SFr	Pt	Bld	Qn	IFCC	mmol/ mol

MFr = Mass Fraction, **MCnc** = Mass Concentration, **MFR.DF** = Mass Decimal Fraction, **SFr** = Substance Fraction, **Pt** = Point in Time, **Bld** = Blood, **Qn** = Quantitative

LOINC

Logical Observation Identifiers Names and Codes (LOINC) is a coding system focused on structured "observations." Most of those observations are laboratory tests, although the LOINC system extends to systematic observations such as radiology reports, clinician rating scales, and tumor registries. It was developed at the Regenstrief Institute of the Indiana University School of Medicine, which developed one of the first U.S.-based electronic medical records in the 1970s. Development began in 1994, and the first list of codes was released in 1996.[1]

LOINC's original developer, Clem McDonald, had previously been a founding developer of the HL7 2.x messaging standard used in virtually all EMRs today. The HL7 2.x standard provided a structure to exchange clinical content, but the widespread use of proprietary codes limited the value of exchanging laboratory orders and results. LOINC set out to solve the problem of reconciling proprietary lists of lab codes from each HL7 message sender and recipient.

LOINC was formally adopted as a code set for HL7 messaging in 1999. LOINC has registered users in 177 countries around the world, with documentation available in 20 languages or linguistic variants. Within the U.S., LOINC has also been adopted as a coding standard for EMR meaningful use regulations and was proposed as a code set for electronic transactions in the HIPAA administrative simplification rules. LOINC has helped individual providers accelerate mapping of their local codes to its standard through the release of RELMA (Regenstrief LOINC Mapping Assistant), an application that facilitates side-by-side comparison of uploaded codes to the LOINC standard.

The numeric part of LOINC codes are structured as one to five digits, a hyphen, and a single check digit. For example, the most frequent code used to describe Hemoglobin A1c tests (as a percentage of total blood) is "4548-4" *(Table 1)*. There is no order or structure to the numeric value before the hyphen, and the allowed digit length may expand once LOINC contains more than 100,000 records. The check digit is a feature allowing message receivers to confirm that the first part of the code is completely and accurately specified.

For each LOINC code, up to six text fields (parts) may be included in the description. These parts include the component (analyte), measurement property, measurement time (duration), body system providing the

measurement sample, measurement scale, and reference method. Separating these parts is an important detail when describing labs, because our lay descriptions of specific labs often combine the analyte with the measurement property ("% hematocrit") or with the timing or sample ("fasting blood glucose") in ways that complicate the grouping and ordering of lab results across a population.

Summarizing laboratory results poses several challenges for the RWE analyst; the structure and taxonomy of LOINC codes helps with some, but not all, of these challenges. The LOINC database stores multiple synonyms for lab tests in addition to the fully specified name, which can help accelerate the mapping of imprecise text descriptions for lab tests. In addition, because many labs are ordered as panels of analytes measured from the same sample, LOINC links codes for the panel (57021-8 for "CBC W Auto Differential panel - Blood") to the (in this case, 30) results typically returned from the panel. Finally, for tests whose results are delivered as categorical values (e.g., tumor stages), LOINC provides standardized codes for answer sets (indicated with a character prefix of "LA") that reduce the risk of alternate spellings disrupting the grouping process ("Stage 4" vs. "Stage IV").

On the other hand, LOINC has developed a fairly open policy for accepting proposals of new lab tests for coding, which has greatly accelerated the scope of tests covered at the expense of enforcing canonical values for tests. That Hemoglobin A1c code above is actually one of nine different values that could be used, with some specifying variants in the reference standard or the analysis method *(Table 1)*. Unlike many of the diagnosis and procedure coding systems with which analysts are familiar, LOINC code values are not logically grouped together (HbA1c values are in a non-contiguous range from "4548-4" to "71875-9"), and while notes in the LOINC database indicate preferences for some codes over others, none are officially deprecated or retired. Therefore, the selection of appropriate codes by an analyst requires careful attention, and often requires consultation of LOINC's published list of the 2,000 most frequent codes observed by ordering volume to determine the preferential values among a range of alternates.

Access to LOINC reference materials is free, with some material requiring the creation of a free user account at https://loinc.org. The online search tool for LOINC codes is at https://search.loinc.org, although downloading the RELMA desktop application offers a few additional features not found in the online search tool. LOINC provides a quick start guide and helpful FAQs, as well as a more detailed user guide both for the LOINC code set and for the RELMA application.

SNOMED CT

SNOMED Clinical Terms (SNOMED CT) is an ambitious attempt to encode the full range of concepts that might be entered in an EMR. It is truly international in nature, resulting from the 1999 merger of one terminology project from the College of American Pathologists (formerly called the **S**ystematized **NO**menclature of **MED**icine), and the READ code project from the UK's National Health Service (NHS).

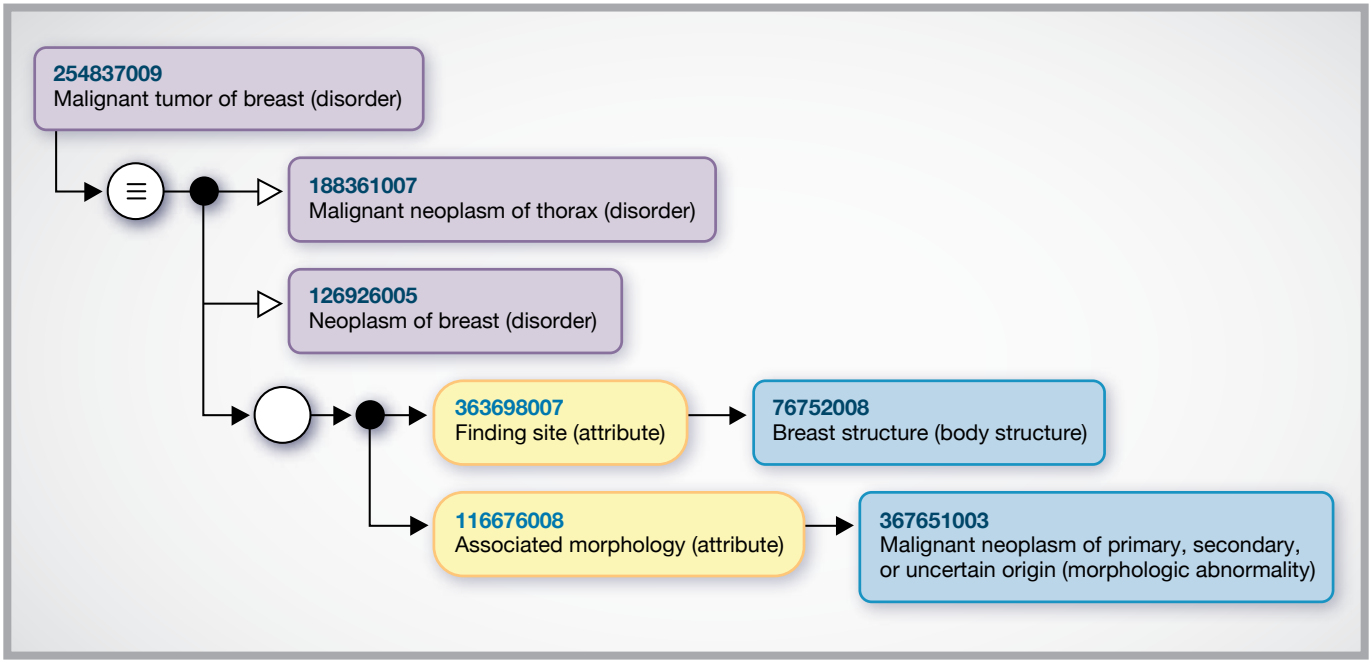
Nine countries with leading roles in health IT created the International Health Terminology Standards Development Organisation (IHTSDO) to acquire the rights to SNOMED CT in 2007. Membership in IHTSDO has since expanded to 24 member countries. Currently, IHTSDO maintains English and Spanish translations of SNOMED descriptions, and member countries have released 8 additional language or dialect translations.

SNOMED codes are between 6 and 18 numeric digits long, and all codes begin with a non-zero digit. Like LOINC, they contain a single check-digit at the end, and

Table 2. SNOMED CT Top Level Domains

Body structure (body structure)
Clinical finding (finding)
Environment or geographical location (environment / location)
Event (event)
Observable entity (observable entity)
Organism (organism)
Pharmaceutical / biologic product (product)
Physical force (physical force)
Physical object (physical object)
Procedure (procedure)
Qualifier value (qualifier value)
Record artifact (record artifact)
Situation with explicit context (situation)
SNOMED CT Model Component (metadata)
Social context (social concept)
Special concept (special concept)
Specimen (specimen)
Staging and scales (staging scale)
Substance (substance)

Figure 1. SNOMED CT Diagram Illustrating Multiple Relationships and Hierarchies for Concept "Breast Cancer"



there is no order or structure to the numeric value of the code. For reasons beyond the scope of this article, SNOMED concept codes also contain a "00" in the second- and third-last digits (e.g., "73211009") that can help the RWE analyst recognize SNOMED concept codes.

Like LOINC, the text description of each code contains a fully standardized name and accepted synonyms. SNOMED CT code 73211009 corresponds to "Diabetes mellitus (disorder)" (fully specified name), "Diabetes mellitus" (preferred synonym), and "DM - Diabetes mellitus" (acceptable synonym). SNOMED CT organizes all of its codes in hierarchies, which include 19 top-level domains *(Table 2)*. The level of organization within these hierarchies varies widely, and is defined by one or more relationships (also with their own SNOMED codes) between concepts. Diagnoses for conditions, for example, are found within the "Clinical finding" domain, but often belong to multiple hierarchies based on relationships to concepts in the "Body structure" domain. To help keep all of this complexity organized, SNOMED has developed a diagramming system to show definitions of key concepts and their relationships *(Figure 1)*. Data analysts will occasionally need to dig into these concepts and relationships when determining which level of a hierarchy to use for selecting codes (and child codes) for a particular research question.

The ambitious scope of SNOMED CT means that its content will overlap with many of the coding systems used for diagnoses, drugs, labs, and procedures. Because of this, IHTSDO has supported multiple projects to map SNOMED CT codes to ICD-9, ICD-10, and LOINC. Other organizations have developed mappings of their own coding systems (e.g., RxNorm) to relevant SNOMED terms. In the near term, this means that one of SNOMED's great values for data analysts will be to offer alternative ways to group concepts when other coding systems fall short.

Access to SNOMED reference materials is free for research use. A variety of reference materials are available at http://www.snomed.org/, ranging from quick start guides all the way to technical implementation guides. The online search tool for SNOMED CT codes is at http://snomed.info/, which includes all of the currently published language translations.

RxNorm

RxNorm is a collection of drug names that have been normalized by the United States National Library of Medicine (NLM). The drug terms have been formalized to represent the primary components of a drug (ingredient[s], strength[s], and dose form) in a standard format, while linking the standardized name to the names found in commonly used drug vocabularies.

The desire to share the variety of existing drug terminologies used by healthcare systems and pharmaceutical manufacturers, and to develop a system to overcome known defects in the existing coding systems (such as National Drug Codes [NDC]) motivated the HL7 Vocabulary Technical Committee in 1998 to develop a better model for representing drug terms. In response, the RxNorm project began in 2002.

Table 3. RxNorm Drug Records Related to "Fluoxetine"

Term type (TTY) Name	Description	Example	RxNorm Concept Unique ID (RXCUI)
Ingredient	A compound or moiety that gives the drug its distinctive clinical properties	Fluoxetine	4493
Precise Ingredient	A specified form of the ingredient that may or may not be clinically active	Fluoxetine Hydrochloride	227224
Multiple Ingredients	Two or more ingredients appearing together in a single drug preparation	Fluoxetine / Olanzapine	406024
Semantic Clinical Drug Component	Ingredient + Strength	Fluoxetine 4 MG/ML	315953
Semantic Clinical Drug Form	Ingredient + Dose Form	Fluoxetine Oral Solution	372232
Semantic Clinical Drug	Ingredient + Strength + Dose Form	Fluoxetine 4 MG/ML Oral Solution	310386
Brand Name	A proprietary name for a family of products containing a specific active ingredient	Prozac	58827
Semantic Branded Drug Component	Ingredient + Strength + Brand Name	Fluoxetine 4 MG/ML [Prozac]	563784

EMR records that utilize RxNorm vocabularies achieve compliance with the 'Meaningful Use' requirements for electronic health records, which has greatly increased adoption in the U.S. RxNorm assimilates drug taxonomies from several global sources to expand the system's reach beyond the U.S.

Each RxNorm concept is identified by an 8-digit Concept Unique ID (RXCUI). Those familiar with existing drug coding systems understand that the existence of combination ingredients, multiple dosing and packaging variants, and different routes of administration, create substantial complexity for how drug concepts are represented and organized. RxNorm assigns RXCUI values at various levels of specificity, called term types or TTYs, in addition to a drug's complete clinical drug name (ingredient, strength, and dose form). Table 3 shows the many different levels at which the antidepressant fluoxetine may be represented, including its appearance in fixed dose combinations.

To manage the links between all of these RXCUIs for a single drug, RxNorm maintains a rich set of relationships among concepts. Each relationship between concept A and B has an exact reverse relationship mapped between concept B and A, as is the case in SNOMED CT. Examples of common relationship pairs in RxNorm include "Has brand name/Brand name of," "Has form/Form of," "Has ingredient/Ingredient of," "Has tradename/Tradename of," "Is a/Inverse is a," and "Has precise ingredient/Precise ingredient of." These relationship links allow analysts to navigate the variety of challenges associated with brand versus generic names; dose, form, and route variations; and fixed dose combinations to select the set of concepts most useful for analysis. However, they also demand greater precision from the analyst to understand which level(s) of specificity is required for selecting the drugs and forms of interest. Selecting RXCUIs usually also requires simultaneously selecting the relevant TTYs, or being prepared to navigate RxNorm's relationship links to filter and capture all the concepts of interest.

The RxNorm datasets and documentation are available for download at no cost from http://www.nlm.nih.gov/research/umls/rxnorm. The National Library of Medicine also provides free access to RxNav, a web-based tool for searching and traversing the RxNorm vocabulary. https://rxnav.nlm.nih.gov/. A desktop version of RxNav is also available for download.

Applications

Analysts working with data that include these newer coding systems will not need to be convinced of the need to understand and use them. An increasing number of data sources are leveraging these code sets to document clinical data, even if the codes were not used in the original data system. This is most clear in the case of datasets formatted for the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM), now maintained by the Observational Health Data Sciences and Informatics (OHDSI) program. The

Table 4. ICD-9 and ICD-10 Concepts Mapped to SNOMED Concept for Breast Cancer in OHDSI ATLAS Browser

Code	Name	Standard?	Domain	Vocabulary
254837009	Malignant tumor of breast	Standard	Condition	SNOMED
174	Malignant neoplasm of nipple and areola of female breast	Non-Standard	Condition	ICD9CM
174	Malignant neoplasm of female breast	Non-Standard	Condition	ICD9CM
174.1	Malignant neoplasm of central portion of female breast	Non-Standard	Condition	ICD9CM
174.2	Malignant neoplasm of upper-inner quadrant of female breast	Non-Standard	Condition	ICD9CM
174.3	Malignant neoplasm of lower-inner quadrant of female breast	Non-Standard	Condition	ICD9CM
174.4	Malignant neoplasm of upper-outer quadrant of female breast	Non-Standard	Condition	ICD9CM
174.5	Malignant neoplasm of lower-outer quadrant of female breast	Non-Standard	Condition	ICD9CM
174.6	Malignant neoplasm of axillary tail of female breast	Non-Standard	Condition	ICD9CM
174.8	Malignant neoplasm of other specified sites of female breast	Non-Standard	Condition	ICD9CM
174.9	Malignant neoplasm of breast (female), unspecified	Non-Standard	Condition	ICD9CM
175	Malignant neoplasm of nipple and areola of male breast	Non-Standard	Condition	ICD9CM
175	Malignant neoplasm of male breast	Non-Standard	Condition	ICD9CM
175.9	Malignant neoplasm of other and unspecified sites of male breast	Non-Standard	Condition	ICD9CM
198.81	Secondary malignant neoplasm of breast	Non-Standard	Condition	ICD9CM
C50	Malignant neoplasm of breast	Non-Standard	Condition	ICD10
C50.0	Malignant neoplasm: Nipple and areola	Non-Standard	Condition	ICD10
C50.1	Malignant neoplasm: Central portion of breast	Non-Standard	Condition	ICD10
C50.2	Malignant neoplasm: Upper-inner quadrant of breast	Non-Standard	Condition	ICD10
C50.3	Malignant neoplasm: Lower-inner quadrant of breast	Non-Standard	Condition	ICD10
C50.4	Malignant neoplasm: Upper-outer quadrant of breast	Non-Standard	Condition	ICD10
C50.5	Malignant neoplasm: Lower-outer quadrant of breast	Non-Standard	Condition	ICD10
C50.6	Malignant neoplasm: Axillary tail of breast	Non-Standard	Condition	ICD10
C50.8	Malignant neoplasm: Overlapping lesion of breast	Non-Standard	Condition	ICD10
C50.9	Malignant neoplasm: Breast, unspecified	Non-Standard	Condition	ICD10

OMOP CDM standardizes data for more interchangeable, globally consistent analyses by relying heavily on these three systems as the standard vocabularies for most clinical facts. Data that are translated into OMOP CDM format have their NDC drug codes converted to RxNorm, their labs converted to LOINC, and their diagnoses converted to SNOMED CT.

OHDSI has created its own browser of codes that can be used within an OMOP CDM, called ATLAS (http://www.ohdsi.org/web/atlas/#/home). This tool allows users to search for specific code values or text descriptions from any of the preferred clinical vocabularies or the non-preferred vocabularies that OHDSI has mapped to them. A search for "diabetes mellitus" returns over 1,000 different records, to which several filters can be applied, including coding system, "domain" (type of clinical fact), and whether the concept is preferred ("standard") in OMOP CDM.

Given the mapping between code sets in ATLAS, the browser has the helpful capability of searching related concepts within and across code sets. This can be useful even if an analyst is working with a dataset that does not contain these newer coding systems. For example, many U.S. data sources in the next several years will include a mixture of ICD-9-CM and ICD-10 diagnosis codes for similar conditions. ICD-9 to ICD-10 mapping schemes exist, but the process of using them can be cumbersome, and there is a reasonable risk of using them improperly.

However, the cross-mappings available in ATLAS can permit users to start with concepts that are closer to their concept of interest, and then find the mapped values in their code sets of interest.

For example, selecting the SNOMED CT code for "Malignant tumor of breast (disorder)" (254837009), and then selecting its related concepts within the ATLAS browser, identifies the 14 distinct ICD-9-CM codes and the 10 ICD-10 codes that have been directly mapped *(Table 4)*. Indeed, if the analyst also needed to find codes to replicate the analysis in a British data source, the same search could be used to select the 31 READ codes linked to the same SNOMED concept.

Despite its power, the ATLAS browser has its limitations when exploring the utility of these newer code sets. The browsers specific to each code do a better job of preserving some of the more detailed documentation and the concept relationships within each code set. The SNOMED browser represents its synonyms and concept diagrams better than ATLAS; the LOINC browser excels at linking analytes to their panels and answer sets; and, the RxNav application includes RXCUI values at more TTY levels than does ATLAS. Analysts will be well served by toggling between each code set's own browser and the ATLAS browser to narrow down the clinical concepts most useful to their research question.

Conclusions

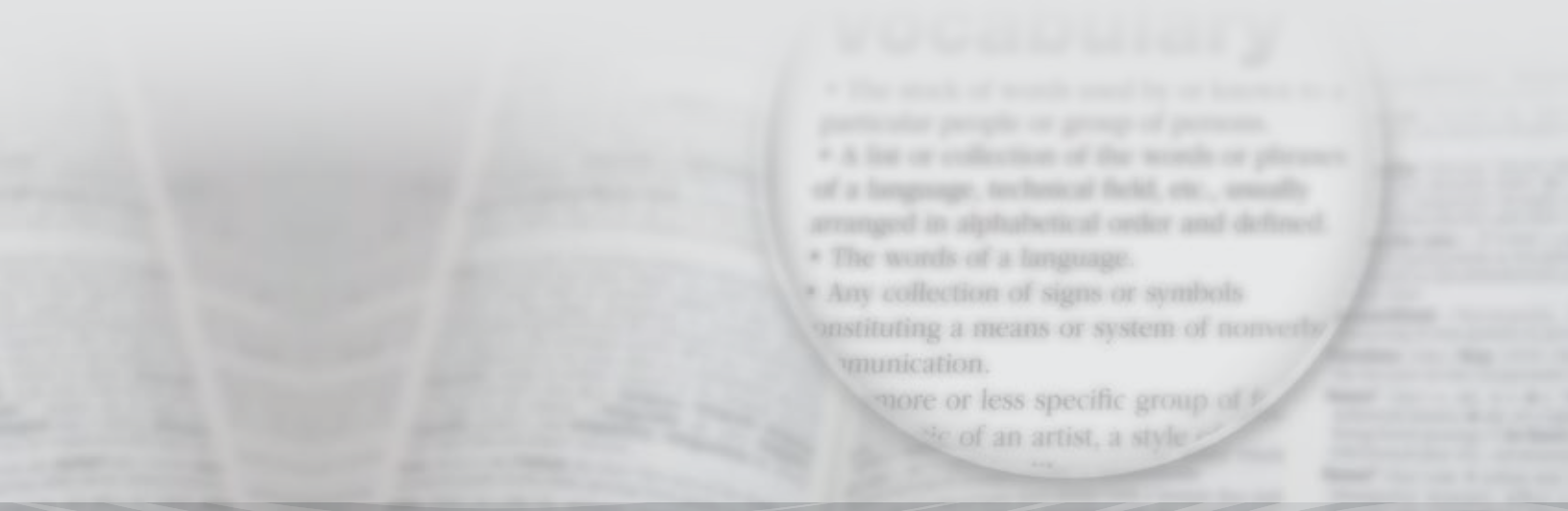
An increasing number of provider-based data sources use or reference global code sets such as LOINC, SNOMED CT, and RxNorm. Local systems are turning to global code sets because of pressure to exchange clinical information with other providers' data systems, and are often incentivized to use global codes by payers or regulatory authorities. As RWE analyses increase in complexity, command of these code sets will become a foundational skill for the RWE analyst. Conversion of databases to common data models will also accelerate the importance of understanding global code sets in greater detail.

As we have shown, however, understanding these global codes can help manage confusion inherent in traditional local code systems, even before they appear in a desired data source. The mapping initiatives required to make these code sets global can assist the RWE analyst with code translation and replication. The hierarchies and other relationships embedded in global code sets can also help the RWE analyst define concepts more precisely without reliance on local billing or coding experts. Free tools and documentation exist for learning most of these code sets, as well as understanding their overlap and relationships to older coding systems. Few barriers exist to developing the coding skills required of the next generation RWE analyst! ■

For more information, please contact Don.O'Hara@evidera.com or Vernon.Schabert@evidera.com.

REFERENCE

[1] Forrey AW, McDonald CJ, DeMoor G, Huff SM, Leavelle D, Leland D, Fiers T, Charles L, Griffin B, Stalling F, Tullis A, Hutchins K, Baenziger J. Logical Observation Identifier Names and Codes (LOINC) Database: A Public Use Set of Codes and Names for Electronic Reporting of Clinical Laboratory Test Results. *Clin Chem.* 1996 Jan; 42(1):81-90.



Evidera Presents at ISPOR's 22ND Annual International Congress

MAY 20 - 24, 2017 – BOSTON, MASSACHUSETTS, USA

SHORT COURSES

Sun., May 21, 2017, 8:00 AM - 12:00 PM

Using DICE Simulation for Health Economic Analyses

Instructors: Caro JJ, Moller J

Sun., May 21, 2017, 1:00 - 5:00 PM

Using Multi-Criteria Decision Analysis in Health Care Decision Making: Approaches & Applications

Instructors: IJzerman MJ, **Marsh K**, Devlin N

WORKSHOPS

BREAKOUT SESSION
Mon., May 22, 2:15 - 3:15 PM

W3: Developing Cost-Effectiveness Models to Assess Value of Immuno-Oncology Therapies: Challenges and Approaches

Briggs A, Haddad R, **Muszbek N**, Zhang Y

BREAKOUT SESSION
Tues., May 23, 2:15 - 3:15 PM

W11: Stated Preferences in Drug Evaluation: A Comparative Assessment of the Use of Stated Preference in the United States, Canada, and the European Union

Muhlbacher AC, **Marsh K**, Johnson FR, Marshall D

BREAKOUT SESSION
Tues., May 23, 3:45 - 4:45 PM

W13: ISPOR Clinical Outcome Assessment Measurement in Rare Disease Clinical Trials Emerging Good Practices Task Force - A Case Study on Application of Final Recommendations

Patrick DL, Perfetto EM, Benjamin K, **Vernon MK**

ISSUE PANELS

BREAKOUT SESSION
Mon., May 22, 2:15 - 3:15 PM

IP5: Voices and Echoes: What Methods Should We Be Using to Capture the Patient Voice?

Hamed A, **Marsh K**, Gwaltney C, Bridges JFP

KEY
Bold Black = Evidera staff member
Bold Purple = PPD staff member

BREAKOUT SESSION
Wed., May 24, 1:45 - 2:45 PM

IP20: Valuing Precision: How Will Next Generation Diagnostics Change the Landscape for HEOR and Patient Management?

Faulkner EC, Husereau D, Zah V, Poulios N

FORUM

BREAKOUT SESSION
Tues., May 23, 6:15 - 7:15 PM

F9: Health Economic Modeling in Oncology

Muszbek N, Benedict A, Wolowacz S

PODIUM PRESENTATION

BREAKOUT SESSION
P14: PATIENT PREFERENCE STUDIES
Tues., May 23, 3:45 - 4:45 PM

PP4: Validation of a Questionnaire to Assess Patient Perceptions of Injection Devices for Type 2 Diabetes

Matza, LS, Stewart, KD, Paczkowski R, **Currie BM, Yu R, Coyne KS**, Boye KS

POSTERS

SESSION I
PHP: HEALTH CARE USE & POLICY STUDIES
Mon., May 22, 8:30 AM - 2:00 PM

PHP272: Reference Groups Used in Pregnancy Exposure Registries: Challenges and Opportunities

Covington D, Buus R, Blum C

PHP 279: REMS Survey Response Rate by Method of Recruitment

Veley K, Covington D, Sites S, Kinard R

SESSION I
PIN: INFECTION
Mon., May 22, 8:30 AM - 2:00 PM

PIN41: Cost-Effectiveness Analysis of First-Line Administration of Tenofovir Alafenamide Fumarate (TAF), a Novel Nucleotide Reverse Transcriptase Inhibitor (NRTI), for the Management of Chronic Hepatitis B (CHB) in the United States (US)

Dusheiko G, Lim J, Liou I, **Tafazzoli A, Deniz B, Saint-Laurent Thibault C**, Gordon S, Nguyen MH

PIN 51: Evaluation of the Performance Properties of the Influenza Patient-Reported Outcomes Instrument (FLU-PRO) in Patients with Influenza-Like Illness (ILI)

Powers J, **Bacci ED, Leidy NK, Stringer S**, Memoli M, Han A, Fairchok MP, Coles C, Owens J, Chen WJ, Arnold JC, Danaher PJ, Lalani T, Hansen EA, Burgess TH, Millar EV, Hernandez A, Rodriguez-Zulueta P, Ortega-Gallegos H, Galindo-Fraga A, Ruiz-Palacios GM, Pett S, Fischer W, Gillor D, Moreno Macias L, DuVal A, Rothman R, Dugas A, Guerrero ML

SESSION II
PCN: CANCER
Mon., May 22, 3:45 - 7:45 PM

PCN15: Efficacy of Treatments in Children with Relapsed/Refractory Acute Lymphocytic Leukemia (R/R ALL): A Systematic Literature Review and Meta-Analysis

Martin AL, Thomas SK, Cota M, Hao Y, **Zhang Y, Turner M**

PCN16: A Bayesian Network Meta-Analysis (NMS) of Therapies for Treatment-Naïve Chronic Lymphocytic Leukemia (TN-CLL) Patients Ineligible for Full-Dose Fludarabine Therapy

Xu Y, Fahrbach K, Dorman E, van Sanden S, Diels J, Cote S, Baculea S

PCN 40: A Review of Epidemiology, Prognosis, and Treatment Options for Recurrent or Metastatic Head and Neck Squamous Cell Carcinomas (HNSCC)

Blieden M, Muszbek N, Chaudhary MA, Zhang Y

PCN115: Comparison of Value Evaluations Using Drug Abacus and Traditional Cost-Effectiveness Analysis for an Immuno-Oncology Drug in an Orphan Indication

Garmo V, **Lanitis T, Ambavane A, Kongnakorn T**, Phatak H

PCN118: Cost-Effectiveness of Ibrutinib as Frontline Treatment for Adult Patients with Chronic Lymphocytic Leukemia in Belgium

Smet A, **Peng S, Dorman E, Deger K, Sorensen S**, Baculae S, Cote S

PCN126: Value Demonstration of Immuno-Oncology Therapies in a Rare Tumor Comparing ASCO, NCCN, and Traditional Cost-Effectiveness Analysis

Garmo V, **Ambavane A, Lanitis T, Kongnakorn T**, Phatak H

PCN177: Understanding Key Symptoms, Side Effects and Impacts of HR+ and HER2- Advanced Breast Cancer: Literature Review and Expert Interviews

Krohe M, Tolley C, Higgins S, Liu Z, Cella D, **Revicki D**, Small T, Tang D

PCN184: Evaluating Clinically Meaningful Change of the EORTC QLQ-C30 in Patients with NSCLC

Lenderking WR, Speck RM, Huang JT, Huang H, Kerstein D, Reichmann W, Langer CJ

SESSION III
PGI: GASTROINTESTINAL DISORDERS
Tues., May 23, 8:30 AM - 2:00 PM

PGI4: Comparative Efficacy and Safety of Tofacitinib and Biologics as Induction Therapy for Moderately-to-Severely Active Ulcerative Colitis: A Systematic Review and Network Meta-Analysis

Rubin DT, **Ashaye AO, Zhang Y, Xu Y, Fahrbach K**, Chen LA, Manuchehri A, Kayhan C, Woolcott JC, Cappelleri JC, Healey P

SESSION III
PND: NEUROLOGICAL DISORDERS
Tues., May 23, 8:30 AM - 2:00 PM

PND29: The Economic Burden of Agitation in Alzheimer's Disease: A Systematic Literature Review

Anatchkova M, Brooks A, Swett L, Harty A, Duffy R, Baker R, Hammer-Helmich L, Sanon Aigbogun M

PND41: Comparison of Institutional Placement between Alzheimer's Disease (AD) Patients in Medicaid and Two AD Registries

Tafazzoli A, Kansal A

SESSION III
PSY: SYSTEMIC DISORDERS/ CONDITIONS
Tues., May 23, 8:30 AM - 2:00 PM

PSY32: Budget Impact Analysis of Eliglustat for Treatment of Gaucher Disease Type 1 in the United States

Nalysnyk L, Sugarman R, **Ward A**

PSY94: Incorporating Patient Input in Selecting Patient Reported Outcomes Instruments for Clinical Studies in Multiple Myeloma

Fleming S, Eremenco S, **Gleeson S, Brooks A**, Chiou CF

KEY
Bold Black = Evidera staff member
Bold Purple = PPD staff member

PSY135: Systematic Literature Review of the Economic Burden Associated with Diffuse Large B Cell Lymphoma and Follicular Lymphoma

Galaznik A, Bell J, **Huelin R, Hoog M, Bhagnani TD, Guo Y, Stokes ME**, Seal B, Shou Y

PSY143: Rare or Next Competitive Landscape

Pereira L, Faulkner EC

SESSION IV
PCV: CARDIOVASCULAR DISORDERS
Tues., May 23, 3:45 - 7:45 PM

PCV61: Cost-Effectiveness Analysis of Dabigatran versus Rivaroxaban for Non-Valvular Atrial Fibrillation Using Real-World Evidence in Medicare Beneficiaries

Peng S, Deger K, Ustyugova AA, Gandhi P, **Qiao N**, Wang C, **Kansal A**

SESSION IV
PMD: MEDICAL DEVICES/ DIAGNOSTICS
Tues., May 23, 3:45 - 7:45 PM

PMD110: The Need for Payer Coverage of Large Next Generation Sequencing Panel Testing in Epilepsy: Potential for Missed Diagnoses Using a Small Gene Panel Approach

Spinner DS, Cardeiro D, Stanley CM, Le NM, Head HA, Scacheri CA, Schuette JL, Pineda-Alvarez DE, Zare AS, Smith D, **Faulkner EC**

SESSION IV
PUK: URINARY/KIDNEY DISORDERS
Tues., May 23, 3:45 - 7:45 PM

PUK19: Health Economic Assessment of Treatment Sequences for the Management of Patients with Metastatic Renal Cell Carcinoma in the United States

Doleh, Y, **Deniz B, Ambavane A, Rao S, Page V**, Michaelson MD

SESSION V
PHS: HEALTH SERVICES
Wed., May 24, 8:00 AM - 1:30 PM

PHS59: Economic Burden of Very Preterm Birth: A Systematic Literature Review

Sarda SP, **Abogunrin S, Zhang Y, Sarri G**

PHS79: Utilization and Cost of Healthcare Services During Episodes of Acute Bacterial Skin and Skin Structure Infections (ABSSSI) Involving Admission To United States (US) Hospitals: A Retrospective Observational Analysis Using A Large Healthcare Claims Database

Keyloun KR, **Murphy B**, Gillard P, **Berger A**

SESSION V
PRM: RESEARCH ON METHODS
Wed., May 24, 8:00 AM - 1:30 PM

PRM5: Real-World Evaluation Screening Study and Registry of Dyskinesia in Patients Taking Antipsychotic Agents: The Re-Kinect Study

Yeomans K, Lenderking WR, Ross L, **Shalhoub H**, Yonan C

PRM60: Machine Learning Integration with Molecular Diagnostics: Progress and Potential Pitfalls

Ringo MC, Faulkner E

PRM87: Exploring Python for Use in Modeling: Decreasing Run-Times for Probabilistic Sensitivity Analysis

Stokes ME, Quon P

PRM98: Why Isn't It The Norm To Use Normal In PSA?

Oguz M, Roiz J

PRM135: Content Validity of the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ) Among Chronic Pain Patients

Coyne K, Barsdorf A, **Brooks A,** Maziere JY, Pierson R, Butler S, Schnoll S

PRM170: Barriers and Solutions for Real-World Chart Review Evidence Generation

Stein D, Ross L

PRM193: Nuances of Assessing Clinician Agreement in Clinician Reported Outcomes (CLINROS)

Bender R, Lenderking W

Upcoming Presentations

ATS 2017

May 19-24, 2017; Washington, DC, USA

POSTER

The Short-Term Impact of Symptom-Defined COPD Exacerbation Recovery on Health Status and Lung Function

Murray L, Leidy NK

ORAL PRESENTATION

EXACT-PRO and Measuring Exacerbations in COPD

Murray L

American Psychiatric Association Annual Meeting

May 20-24, 2017; San Diego, CA, USA

POSTER

Early vs. Later Treatment Response in Lurasidone-Treated Patients with Bipolar Depression: Association with Patient-Reported Health Outcomes

Ng-Mak D, **Bacci ED, Poon JL,** Rajagopalan K, Loebel A

McGill University, Faculty of Medicine | Summer Session 2017

May 29-June 1, 2017; Montreal, Canada

SHORT COURSE

EPIB-654 PE IV: Pharmacoeconomics Summer Course

Caro JJ

HTAi 2017 Annual Meeting

June 17-21, 2017; Rome, Italy

WORKSHOP

Discretely-Integrated Condition Event (DICE) Simulation for Integrated HTA

Caro JJ, Moller J

KEY

Bold Black = Evidera staff member

Bold Purple = PPD staff member

SYMPOSIUM

Changing the HTA Paradigm: Beyond Clinical and Economic Evaluation for Innovative Drugs

Chevrou-Severac H, **Caro JJ**, Walker A, de Pouvourville G, Formica M

ISSUE PANEL

Validation of Health Economic Models: Should We Promote a Pragmatic Approach?

Caro JJ, Moller J, Ghabri S, Stevenson M, Kolominsky-Rabas P

Rules of Engagement: Motivations for Engaging Patients in HTA Decisions

Caro JJ, Sandman L, Kolominsky-Rabas P, Hamed A, Mertens R

DIA 2017 Annual Meeting

June 18-22, 2017; Chicago, IL, USA

CHAIR/SPEAKER

Patient-Reported Outcomes (PROs): Hot Topics - Part 2 of 2

Revicki D

Due Diligence in Mergers and Acquisitions (M&A)

Chen D

SPEAKERS

2.5 Billion Opinions from 50 Million Health Care Users: A Guide to Health-Related Social Media

Cox AP

An Innovative Patient-Centric Approach to Conducting Postmarketing Safety Studies

Covington D

Developing and Evaluating PRO Instruments in Clinical Trials: Risks and Advantages for Applications using Registration Trials

Revicki D

Innovative Approaches for Conducting a Lactation Study

Hurst N

Incorporating Patient Preferences in Drug Development and Approval

Marsh K

Lessons Learned From the EMA Adaptive Pathways Pilot Project: The Need for a Real-world Data Strategy for Success

Lambrelli D

Take-Home Learnings on Do's and Don'ts on the Planning and Conduct of a PASS

Cid J

POSTERS

Retrospective Chart Review Studies: Opportunities and Challenges to Post-Market Evidence Generation

Stein D, Ross L

Trends in Response Rate for Recurrent REMS Surveys

Veley K

ISPOR 6th Latin America Conference

Sept. 15-17, 2017; Sao Paulo, Brazil

SHORT COURSE

Modelación Aplicada (Applied Modeling)

Caro JJ, Mejia A

ISSUE PANEL

Multi-Criteria Decision Analysis (MCDA) in Latin America

Valentim J, Garau M, **Caro JJ**, Murta Amaral L

Recent Presentations

Heart Rhythm 2017

May 10-13, 2017; Chicago, IL, USA

POSTER

Development and Validation of the AFImpact: An Atrial Fibrillation-Specific Measure of Patient-Reported Health-Related Quality of Life

Edvardsson NG, **Coyne KS,** Ryden A

6th Bordeaux Pharmacoepi Festival

May 10-12, 2017; Bordeaux, France

SESSION SPEAKER

The Use of DICE Simulation for Epidemiologic Models

Caro JJ

Pediatric Academy Societies Meeting

May 6-9, 2017; San Francisco, CA, USA

POSTER

Prevalence of Long-Term Neurodevelopmental Impairment Associated with Extreme Prematurity in North America: A Systematic Literature Review

Sarri G, Abogunrin S, Siffel C, Sarda SP

ISCT 2017

May 3-6, 2017; London, UK

TRACK SESSION

Cost, Price and Market Access: Putting the Pieces Together in an Industry Model

Driscoll D, MacKay G, Hodgkin K, **Faulkner E**

Canadian Respiratory Conference 2017

April 27-29, 2017;
Montreal, Quebec, Canada

POSTER

Effect of 8 and 12 Weeks' Once-Daily Tiotropium and Olodaterol, Alone and Combined with Exercise Training, on Exercise Endurance during Walking in Patients with COPD

Troosters T, Bourbeau J, Maltais F, **Leidy N**, Erzen D, De Sousa D, Korducki L, Janssens W, Hamilton A

Access Europe Summit 2017

April 25-26, 2017;
Amsterdam, The Netherlands

ORAL PRESENTATION

Pressure on Prices - Dealing with a Shifting Landscape

Pruce D

Quality of Care and Outcomes Research 2017 Scientific Session

April 2-3, 2017; Arlington, VA, USA

POSTERS

Adherence to Rivaroxaban Compared to Other Oral Anticoagulant Agents among Patients with Non-Valvular Atrial Fibrillation

McHorney CA, Ashton V, Laliberté F, Germain G, Wynant W, Crivera C, Schein J, Lefebvre P Peterson ED

Adherence to Rivaroxaban versus Apixaban among Patients with Atrial Fibrillation: Analysis of Overall Population and Subgroups of Prior Oral Anticoagulant Users

McHorney CA, Crivera C, Laliberté F, Germain G, Wynant W, Lefebvre P

Impact of Differences in Once- vs. Twice-Daily Medication Adherence on the Risk of Bleed and Stroke in Non-Valvular Atrial Fibrillation: Analysis of Randomized Trials and Claims Data Sources

McHorney CA, Peterson ED, Durkin M, Ashton V, Laliberté F, Crivera C, Sheikh N, Germain G, Schein J, Xiao J, Lefebvre P

La Universidad Javeriana | Clinical Epidemiology PhD Program

March 30-April 1, 2017;
Bogota, Colombia

WORKSHOP

Cambiando el Paradigma: simulación por Condición y Eventos Discretamente Integrados (CEDI©) para ETS

Caro JJ

AMCP Managed Care & Specialty Pharmacy Annual Meeting 2017

March 27-30, 2017; Denver, CO, USA

POSTERS

The Burden of Severe Hypoglycemia in Type 1 Diabetes

Liu J, Wang R, Ganz ML, Paprocki Y, Weatherall J

The Burden of Severe Hypoglycemia in Type 2 Diabetes

Liu J, Wang R, Ganz ML, Paprocki Y, Weatherall J

TSANZSRS 2017

March 24-28, 2017; Canberra, Australia

ORAL PRESENTATIONS

Bronchodilator Therapy and Exercise Added to Self-Management Behaviour-Modification: Effects on Physical Activity in COPD

Troosters T, Maltais F, **Leidy N**, Lavoie K, Sedeno M, Janssens W, Hamilton A, Erzen D, De Sousa D, Korducki L, Bourbeau J

Effect of Tiotropium and Olodaterol, Alone and with Exercise Training, on Exercise Endurance in COPD

Troosters T, Bourbeau J, Maltais F, **Leidy N**, Erzen D, De Sousa D, Korducki L, Janssens W, Hamilton A

58th Congress of the DGP

March 22-25, 2017; Stuttgart, Germany

POSTERS

Effect of 8 and 12 Weeks' Once-Daily Tiotropium and Olodaterol, Alone and Combined with Exercise Training, on Exercise Endurance during Walking in Patients with COPD

Troosters T, Bourbeau J, Maltais F, **Leidy N**, Erzen D, De Sousa D, Korducki L, Janssens W, Hamilton A

Effects of Bronchodilator Therapy and Exercise Training, Added to a Behaviour-Modification Programme, on Physical Activity in COPD

Troosters T, Maltais F, **Leidy N**, Lavoie K, Sedeno M, Janssens W, Hamilton A, Erzen D, De Sousa D, Korducki L, Bourbeau J

ACC.17: 66th Annual Scientific Session & Expo 2017

March 17-19, 2017;
Washington, DC, USA

POSTERS

Rivaroxaban Users Have Significantly Less Treatment Discontinuation Compared with Users of Other Oral Anticoagulants in Non-Valvular Atrial Fibrillation

McHorney CA, Ashton V, Laliberté F, Germain G, Wynant W, Crivera C, Schein J, Lefebvre P, Peterson, ED

DIA Statistics Community Webinar

March 17, 2017; Online

WEBINAR

Developing PRO Instruments in Clinical Trials: Issues, Considerations and Solutions

Kammerman L, Johnson LL, Chen WH, **Revicki D**, Coon C

American Academy of Pain Medicine Annual Meeting

March 16-19, 2017; Orlando, FL, USA

POSTER

Efficacy and Safety of Naloxegol for OIC in Patient Subgroups Defined by Specific Opioid Medication, Opioid Dose, and Duration of Opioid Use

Nalamachu S, Gudin J, Datto C, Hu Y, **Coyne K, Poon JL**

DIA Medical Affairs and Scientific Communications Forum

March 15-17, 2017; Tucson, AZ, USA

POSTER

Regulatory Cross-training Program for Post-approval Medical Writers: Embracing Transferrable Skills and Clinical Expertise

Maya-Perez Y, Kim S, Froom E, Cash K

American Academy of Dermatology Annual Meeting

March 3-7, 2017; Orlando, FL, USA

POSTERS

Patients' Perspectives on the Impact of Moderate-to-Severe Genital Psoriasis

Cather JC, Bleakman AP, Naegeli A, **Poon JL**, Wallace A, Hollister K, Fretzin S

The Burden of Moderate-to-Severe Genital Psoriasis: Patients' Perspective on Symptoms

Ryan C, Meeuwis K, Bleakman AP, Naegeli A, **Poon JL**, Hollister K, Fretzin S

16th International Myeloma Workshop

March 1-4, 2017; New Delhi, India

POSTER

Efficacy of Daratumumab-based Regimens in Patients with Relapsed/Refractory Multiple Myeloma - A Systematic Literature Review and Network Meta-Analysis

Dimopoulos MA, Weisel K, Kaufman J, Sonneveld P, **Rizzo M, Xu Y, Fahrbach K**, Gaudig M, Slavcev M, Dearden L, Lam A

HNC World Pharma Pricing and Market Access 2017

February 22-23, 2017; London, UK

SPEAKER

The Balancing Act of Providing Fast Access to Breakthrough Medicines and Ensuring Evidence-based Decision-Making

Michel S

12th Congress of ECCO - Inflammatory Bowel Diseases

February 15-18, 2017; Barcelona, Spain

POSTER

Comparative Effectiveness Analysis of Flares, Hospitalisations, and Corticosteroid Use among Biologic-Naïve Patients with Inflammatory Bowel Disease within 12 Months of Initiation of Vedolizumab or Infliximab

Alam N, **Raluy-Callado M**, Gardstein B, Curtis R, Khalid JM

ORAL PRESENTATION

Vedolizumab (VDZ) and Anti-TNFα Treatment Effectiveness in Patients with IBD Treated in Germany: A Retrospective Chart Review

Ehehalt R, Schubert S, **Stein D, Lambrelli D**, Bassel M, Orzechowski HD, Minda K, Khalid JM

Congres de Pneumologie de Langue Francaise

January 27-29, 2017; Marseille, France

POSTER

Effet de l'Association Tiotropium et Olodaterol Prise Une Fois Par Jour Pendant 8 et 12 Semaines, Seule et Combinée à l'Entraînement Physique, sur l'Endurance à l'Exercice Lors de la Marche Chez les Patients Atteints de BPCO

Troosters T, Bourbeau J, Maltais F, **Leidy N**, Erzen D, De Sousa D, Korducki L, Lavoie KL, Janssens W, Hamilton A, Derom E

2017 Gastrointestinal Cancers Symposium

January 19-21, 2017;
San Francisco, CA, USA

POSTER

Thromboembolic Events among Patients with Metastatic Pancreatic Ductal Adenocarcinoma after Chemotherapy

Lyman GH, **Schabert VF**, Philip PA, **Stokes M, Bhurke S**, Kuderer NM, Qadan A, Khorana A

AIBD | 2016

December 8-10, 2016; Orlando, FL, USA

POSTERS

Corticosteroid Use in Patients with Crohn's Disease Initiating Vedolizumab in the Real-World Setting

Sands BE, Khalid JM, Barocas M, **Raluy-Callado M, Merinopoulou E**

Hospitalisations, Flares, and Corticosteroid Use Outcomes in Biologic-Naïve Patients with Ulcerative Colitis and Crohn's Disease Initiating Vedolizumab

Alam N, **Raluy-Callado M, Donaldson R**, Kaviya A, Khalid JM

Treatment Patterns of Vedolizumab and Anti-TNF-α Use among Patients with UC and CD in Germany: A Multicenter Retrospective Chart Review

Ehehalt R, Schubert S, **Stein D, Lambrelli D**, Ramagopalan S, Bassel M, Orzechowski HD, Minda K, Khalid JM

CTAD 9th Clinical Trials on Alzheimer's Disease

December 8-10, 2016; San Diego, CA, USA

POSTER

Effects of Potentially Selective End of Follow-up in a Population with Late Mild Cognitive Impairment Using a Disease Simulation

Kansal A, Tafazzoli A, Krotneva M, Dos Santos R, **Ishak KJ**

British Thoracic Society Winter Meeting

December 7-9, 2016; London, UK

POSTER

The Development and Psychometric Validation of the Early Morning Symptoms of COPD Instrument (EMSCI)

Hareendran A, Zaiser E, Make B, Garcia Gil E

ORAL PRESENTATION

Effect of 8- and 12-Weeks' Once-Daily Tiotropium and Olodaterol, Alone and Combined with Exercise Training, on Exercise Endurance during Walking in Patients with COPD

Troosters T, Bourbeau J, Maltais F, **Leidy N**, Erzen D, De Sousa D, Korducki L, Lavoie KL, Janssens W, Hamilton A

ASH 58th Annual Meeting and Exposition

December 3-6, 2016; San Diego, CA, USA

POSTERS

Current Diagnosis Patterns for Acute Myeloid Leukemia (AML) in Clinical Practice Compared with World Health Organization (WHO) 2008 Recommendations: Outcomes from the CONNECT® Myelodysplastic Syndromes (MDS) and AML Disease Registry

George TI, Erba HP, Steensma DP, Pollyea DA, Abedi M, Bejar R, Cogle CR, Garcia-Manero G, Grinblatt D, Komrokji R, Maciejewski J, **Revicki D**, Roboz GJ, Savona MR, Scott B, Sekeres MA, Thompson MA, Fliss A, Swern AS, Nifenecker M, Kiselev P, Sugrue MM, Foucar K

Economic Evaluation of Carfilzomib+Dexamethasone (Kd) vs. Bortezomib+Dexamethasone (Vd) in Relapsed or Refractory Multiple Myeloma (R/RMM)

Jakubowiak AJ, **Houisse I**, Majer I, **Benedict A**, Campioni M, Panjabi S, Ailawadhi S

PODIUM

Economic Burden of Acute Graft-Versus-Host Disease (GvHD) Following Allogeneic Hematopoietic Cell Transplant (HCT) for Hematologic Malignancies

Grubb W, **Huse S**, Alam N, Dychter S, Wingard JR, Majhail NS, **Berger A**

American Heart Association Scientific Session

November 12-16, 2016; New Orleans, LA, USA

POSTERS

Outcomes and Costs of Remote Patient Monitoring among Patients with Implanted Cardiac Defibrillators: An Economic Model Based on the PREDICT RM Database

Hummel JP, **Leipold RJ**, Amorosi SL, Bao H, **Deger KA**, Jones PW, **Kansal AR**, Ott LS, **Stern S**, Stein K, Curtis JP, Akar JG

Which Oral Anti-Coagulant Do Patients Prefer for Stroke Prevention in Non-Valvular Atrial Fibrillation?

Lip GYH, Verdecchia P, **Tervonen T**, Ustyugova A, Heinrich-Nols J, Gropper S, Kwan R, **Sri Bhashyam S, Marsh K**

17th Annual Las Vegas Dermatology Seminar

November 10-12, 2016; Las Vegas, NV, USA

POSTER

A Systematic Review of Real-World Effectiveness of Biologic Switching in Psoriasis

Feldman SR, **Turner MTB**, Zhao Y, Hur P, Herrera V, **Martin AL**

Publications

Alberti A, Lacoin L, Morais E, Lefevre C, **Abogunrin S, Iheanacho I**. Literature Review of the Distribution of Hepatitis C Virus Genotypes across Europe. *J Med Virol.* 2016 Dec; 88(12):2157-2169. doi: 10.1002/jmv.24573.

Augustovski F, **Caro J**, Ferraz MB, Zarate V. Pharmacoeconomics, Outcomes Research, Health Technology Assessment, Comparative Effectiveness, Patient Centered Outcomes Research in Latin America 2016: Brief Update. *Value Health Reg Issues.* 2016 Dec; 11:74-75. doi: 10.1016/j.vhri.2016.11.001.

Bacci ED, Wyrwich KW, Gries KS, Chen Y, Jain R, Konkol L, Merilainen MJ, Weng HH. An Adaptation of the Profile of Mood States for Use in Adults with Phenylketonuria. *Journal of Inborn Errors of Metabolism & Screening.* 2016 Jan-Dec; 4. doi: 10.1177/2326409816669373.

Bacci ED, Wyrwich KW, Phillips GA, Vollmer T, **Guo S**. Analysis of the Psychometric Properties of the Multiple Sclerosis Impact Scale-29 (MSIS-29) in Relapsing-Remitting Multiple Sclerosis Using Classical and Modern Test Theory. *Mult Scler J Exp Transl Clin.* 2016 Oct; 2:1-13. doi: 10.1177/2055217316673235.

Browne C, Lanitis T, Hamilton M, Li X, Horbyluk R, Mardekian J, **Kongnakorn T**, Cohen A. Impact of Apixaban vs Low Molecular Weight Heparin/Vitamin K Antagonist on Hospital Resource Use in Patients with Venous Thromboembolism. *J Med Econ.* 2017 Jan; 20(1):98-106.

Bytzer P, Reimer C, Smith G, **Anatchkova MD, Hsieh R**, Wilkinson J, Thomas SJ, **Lenderking WR**. Psychometric Evaluation of a Daily Gastro-oesophageal Reflux Disease Symptom Measure. *Scand J Gastroenterol.* 2017 Mar; 52(3):276-283. doi: 10.1080/00365521.2016.1250282.

Caro J. Reply: Letter to the Editor: About the Advantages and Disadvantages of Discrete-Event Simulation for Health Economic Analyses. *Expert Rev Pharmacoecon Outcomes Res.* 2016 Dec; 16(6):653.

Caro JJ. Response to Letter to the Editor Regarding Discretely Integrated Condition Event Simulation for Pharmacoeconomics. *Pharmacoeconomics.* 2016 Nov; 34(11):1189-1190.

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Celli B, Tetzlaff K, Criner G, Polkey MI, Sciurba F, Casaburi R, Tal-Singer R, **Kawata A**, Merrill D, Rennard S; COPD Biomarker Qualification Consortium. The 6-Minute-Walk Distance Test as a Chronic Obstructive Pulmonary Disease Stratification Tool. Insights from the COPD Biomarker Qualification Consortium. *Am J Respir Crit Care Med.* 2016 Dec 15; 194(12):1483-1493.

Ciomek K, Kadzinski M, **Tervonen T**. Heuristics for Prioritizing Pair-Wise Elicitation Questions with Additive Multi-Attribute Value Models. *Omega (Westport).* [In Press]

Coyne KS, Currie BM, Donevan S, Brodsky M, Asmus MJ, Krichbaum DW, Cappelleri JC, Hegeman-Dingle R, Sadosky A, Whipple SZ, Burbridge C, Mulhem E, Hillenberg JB. Psychometric Validation of the Electronic Chronic Pain Questions (eCPQ) in a Primary Care Setting. *Curr Med Res Opin.* 2017 Jan; 33(1):137-148.

Coyne KS, Currie BM, Donevan S, Cappelleri JC, Hegeman-Dingle R, Abraham L, **Thompson C**, Sadosky A, Brodsky M. Discriminating between Neuropathic Pain and Sensory Hypersensitivity using the Chronic Pain Questions (CPQ). *Postgrad Med.* 2017 Jan; 129(1):22-31. doi: 10.1080/00325481.2017.1267538.

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Evidera and PPD - Stronger Together

Together we are able to provide unique and integrated solutions that have the greatest impact for our clients. Read what some of our experts have to say about the opportunities they have seen so far.

"We are excited to be part of PPD and amazed at the opportunities we are finding to work together. From strategic study design to dissemination, regulatory challenges to market access, single studies to comprehensive asset programs, pre- to post-approval, our complementary skill sets enable us to offer clients a full range of services across many therapeutic areas."

Nancy Kline Leidy, PhD
Senior VP, Scientific Affairs, Evidera

"I have been really pleased to see the synergies between the teams and how quickly everyone has integrated into the "one-team" approach, working together on real-world studies that integrate Evidera's scientific and strategic leadership and PPD's operational excellence. Functioning as one team has allowed us to show our clients our combined capabilities and solution-focused approach and demonstrate we are the best partner for them in the peri/post-approval space. The commitment to collaboration and the clear collaborative spirit we have seen internally has been exceptional. I see so much potential for what we can accomplish as we move forward."

Les Enterline
Global Head, Medical Affairs Research Operations, PPD

"The work we have been doing on simulating Alzheimer's disease progression, and clinical trials in general, is now taking on even more significance as we see opportunities to collaborate with PPD to offer clients insight into their trial designs. Simulating trial outcomes can help quantify the trade-offs and potential outcomes of alternative trial designs and allow companies to anticipate results and make decisions accordingly."

Anuraag Kansal, PhD
Senior Research Leader and Director, Disease and Trial Simulation, Modeling and Simulation, Evidera

"Evidera and PPD have both been focusing heavily on rare and orphan diseases and the unique challenges that exist with getting these treatments approved and accessible. Being able to share knowledge and resources has been particularly helpful as we work with clients to develop the value proposition for their products in this space, including outreach to patient advocacy groups and investigating ways to better include patients and caregivers into studies. We are already working together on multiple projects where we are leveraging both strategic and operational abilities and seeing positive results."

Dawn Phillips, PhD
Research Scientist, Outcomes Research, Evidera

"The oncology drug development pipeline is expanding, with advances in biotechnology creating new development opportunities while at the same time making the clinical trial landscape much more complex. Working with Evidera colleagues has fostered a lot of potential to optimize protocol development and operations in oncology trials, including better anticipation of post-approval needs that can be integrated earlier into trial designs. It is exciting to think we can support R&D clients with information in early stages of development to design trials that will also provide crucial data for activities focused on market access."

Dirk Reitsma, MD
Vice President, Head of Oncology Global Product Development, PPD

"Regulators and payers require both unique and complementary evidence, and being able to guide clients in the early planning stages on how to design studies to gather the necessary information for both approval and market access is extremely important to maximize the asset value. Strategic alignment and effective management of these converging disciplines creates effective solutions for more robust and complete evidence packages, enabling clients to realize efficiencies that result in time and cost savings. Working with Evidera to identify those market access needs allows us to insightfully guide our clients more effectively in their trial design and registration strategy to optimize the value of their products across the entire lifecycle."

Elizabeth Madichie, PhD
Global Head of Regulatory Affairs, PPD

"We are seeing patient advocacy groups and patient consultants taking a larger role in the drug development process, specifically in the setting of research agendas, identifying current unmet needs, selecting and developing clinical trial endpoints, and informing trial design. PPD and Evidera both have experience working with patient advocacy groups and patient consultants, and by sharing these resources and discussing best practices, we are seeing opportunities to expand our outreach with patients and create novel ways to involve them in studies."

Hilary Wilson, PhD
Research Scientist, Outcomes Research, Evidera

"The integration of PPD's medical writing and healthcare communications team into Evidera was a perfect fit, with immediate areas of synergy obvious. We have always supported medical affairs studies (including real-world and Phase IV) with protocol and study report writing, but seeing how the strategic and operational teams are working together brings more of what we can do to support clients by being an integral part of their team and ultimately meeting our objective to help patients. There are colleagues who write more for a clinician-focused audience, and that brings a new offering to Evidera clients that did not exist here before."

Saurabh Aggarwal, PhD
Medical Writing Team Lead, PPD

"Regulators and payers are increasingly using data on patient preferences and patient-centered benefit-risk assessment to support decisions. Evidera has a team dedicated to supporting our clients in applying these methods. Now as part of PPD, we can bring this expertise to a wider audience, ensuring all of our clients have access to these methods to inform decision making across a product's entire lifecycle, including product development, trial design, approval and reimbursement submissions, and post-launch pharmacovigilance."

Kevin Marsh, PhD
Senior Research Scientist and Executive Director, Outcomes Research, Evidera

"Both PPD and Evidera have strong grounding in emerging and transformative technologies like cell and gene therapy, precision medicine, immunotherapies, orphan disease products, complex combination products, and e-connective applications. Together, we are addressing the unique challenges of these emerging areas with our patient recruitment footprint and clinical expertise, combined with leading health outcomes and market access capabilities. By leveraging data assets and integrator technology like Evalytica, the combined organization is well positioned to take a leadership role as our methodologies and approaches to evidence-based analyses continue to evolve rapidly, allowing us to successfully partner with clients to help navigate these technologies to the market, including areas with limited market precedent."

Eric Faulkner, MPH
Vice President, Precision and Transformative Technology Solutions, Evidera

Evidera Welcomes New Senior Staff

Deborah Covington, DrPH, is a Senior Research Leader, Real-World Evidence for Evidera, providing leadership and strategic direction on registries and observational studies. Dr. Covington transitioned to Evidera from PPD, where she was the Global Head, Observational Studies and Pregnancy Registries leading the late stage group in the conduct of registries and observational studies, with a particular emphasis on patient-centered studies and global pregnancy registries.

Dr. Covington holds a part-time faculty position in the Clinical Research Department at the University of North Carolina, Wilmington. Dr. Covington offers more than 30 years of clinical research experience in epidemiology, observational studies, and registries. Her primary focus involves patient-centric studies (i.e., pregnancy registries, patient registries), studies employing secondary data sources (i.e., national databases and electronic records) and other post-marketing safety studies such as Risk Evaluation and Mitigation Strategies (REMS). She received her doctorate in public health from the University of North Carolina at Chapel Hill, and recently, Dr. Covington was named a Fellow of the International Society of Pharmacoepidemiology.

Dr. Covington has served as a consultant to the World Health Organization and FDA on various aspects of designing and conducting registries. She has over 50 publications in the scientific literature and hundreds of presentations at professional conferences, including papers on best practices for conducting observational studies and registries. She serves as a reviewer for several scientific journals and professional societies and was also invited to write case studies and chapters for *Registries for Evaluating Patient Outcomes: A User's Guide* commissioned by the U.S. Agency for Healthcare Research and Quality (AHRQ), as well as a noted textbook on pharmacoepidemiology.

Anne Delaney, MBA, is Vice President of Real-World Evidence - Europe and General Manager of Syndicated Offerings for Evidera. She is focused on the growth of Evidera's global real-world evidence database offerings, including the linkage between technology and consultative approaches, and the development and implementation of innovative offerings to better identify, anticipate, and support the needs of biopharmaceutical companies.

Ms. Delaney's 25-year career in healthcare has focused on strategy development and deployment with an emphasis on technology-enabled analytics and business intelligence solutions. She has led and fostered international multidisciplinary teams, in both pharmaceutical companies and consultancies, to support the development and validation of strategic plans and commercial decisions for both specific treatment products and companies as a whole. With a keen understanding of client needs, Ms. Delaney has proven success in developing and deploying innovative and commercially viable solutions to meet the changing demands in the marketplace. She began her career at SmithKline Beecham (now GlaxoSmithKline) as an international product manager, and then spent several years with the Pharma Strategy Group in London. She then moved to Datamonitor Healthcare where she led a global team to develop compelling pharmaceutical market analysis data. Ms. Delaney also held vice president roles in portfolio optimization and syndicated analytics for IMS Health, and joins Evidera from GlobalData where she recently held the position of Global Head of Pharma, responsible for the strategic direction and growth of the healthcare business.

Ms. Delaney is a thought leader in the industry and has given numerous presentations on a variety of healthcare topics at conferences, government organizations, and client groups. She received her master of business administration from the London Business School and her bachelor's degree in economics from Trinity College Dublin.

Alex Exuzides, PhD, is a Senior Research Leader, Real-World Evidence, with Evidera. Dr. Exuzides is responsible for the design and implementation of research projects, providing leadership as principal investigator. Many of these projects apply complex and novel methodological approaches in real-world evidence generation, including retrospective database analyses, observational studies, efficacy and safety studies, patient-reported outcomes, pharmacoeconomics, and epidemiologic research.

Dr. Exuzides has over 20 years' experience in research methods in medicine, health services, health economics, comparative effectiveness research, epidemiology, program evaluation, and risk assessment. His therapeutic areas of expertise include cardiovascular, endocrinology, pulmonary/respiratory, and oncology. He is the author of numerous peer-reviewed publications in first-tier journals including *Mayo Clinic Proceedings*, *Epidemiology*, *Biostatistics*, and the *Journal of the American College of Cardiology*.

Dr. Exuzides holds a bachelor of arts in mathematics from the University of Patras, Greece, and a master of arts and doctorate degree, both in statistics, from the University of California at Davis.

Frances C. Macdonald, PhD, is Vice President, Integrated Client Services for Evidera based in London. Dr. Macdonald is focused on developing and implementing integrated services within Evidera, and potentially PPD, in a manner which optimally meets client needs and leverages the strengths which exist across the full portfolio of Evidera services.

Prior to joining Evidera from PPD, where she led the Strategic Partnership account with Roche, Dr. Macdonald spent seven years as a member of the Scottish Medicines Consortium (SMC), the Scottish HTA agency, as the lead industry representative, sponsored by the Association of the British Pharmaceutical Industry (ABPI). As part of the role, she chaired the joint SMC/industry user group forum, ensuring collaboration on the evolution of processes and methods.

Earlier in her career, Dr. Macdonald spent seven years leading European, then global, health economic and outcomes research groups in Syntex (UK) followed by Roche (Basel). Within Roche, her team provided strategic advice plus operational support on health economics and pricing throughout the company, from basic research through to the commercial affiliates. Dr. Macdonald has also worked in a range of roles in clinical development, including project management, clinical pharmacology, and European regulatory affairs, and led a global lifecycle team within the Roche oncology franchise. Dr. Macdonald also established and grew the UK and Irish commercial subsidiary of Actelion. Dr. Macdonald holds a doctorate degree in physiology from Glasgow University.

Ann Mallard, MPH, is a Director, Late Stage Studies with Evidera's Real-World Evidence (RWE) team and is responsible for providing strategic, operational, and day-to-day tactical support to the RWE team. In her role at Evidera, her responsibilities also include providing scientific oversight to studies, preparing study protocols, managing EDC within KeySurvey, and leading analysis and writing deliverables.

Ms. Mallard has over 17 years of experience in clinical research. Prior to joining Evidera, she worked at PPD as a clinical research associate, a biostatistician, and health outcomes scientist in a broad range of therapeutic areas; and, managing and acting as the lead epidemiologist on several pregnancy registries and numerous observational studies. Prior to her employment in the pharmaceutical industry, Ms. Mallard served as a data manager and analyst for the state health department of Georgia. Ms. Mallard also worked as a research coordinator for Emory University and an infection control specialist at Grady Memorial Hospital in Atlanta, Georgia, after earning her Master of Public Health in epidemiology from Emory University.

David Pruce, MRPharmS, is a Senior Principal, Market Access Consulting at Evidera in London. Mr. Pruce leads a London-based team of consultants and analysts supporting clients to address strategic market access, pricing and reimbursement issues.

Mr. Pruce is a former director of policy and communications at the Royal Pharmaceutical Society of Great Britain. He has worked extensively with NICE, MHRA, and other healthcare bodies, including a number of medical Royal Colleges. Mr. Pruce was involved with NICE since its formation, chairing one of NICE's National Collaborating Centres for nearly a decade and sitting on NICE committees. He has expertise across market access and pricing with a particular understanding of the payer perspective.

After running his own consulting company advising the pharmaceutical industry, he joined ICON plc as a principal in pricing and market access. He has developed an interest in cell and gene therapies and how payers will assess and fund them, advising both big pharma and smaller biotech companies on a strategic approach to payer engagement over cell and gene therapies.

Mr. Pruce is a qualified pharmacist and a member of the Royal Pharmaceutical Society. He was a Board member of the Faculty of Pharmaceutical Medicine of the Royal Colleges of Physicians for six years.

Annalisa Rubino, PhD, is a Senior Research Scientist at Evidera. Dr. Rubino has over 20 years of experience in drug development within the academic, government, and industry environments. At Evidera she works in the Real-World Evidence group, providing expertise in observational studies and therapeutic risk management, including post-authorization safety studies (PASS) and risk minimization interventions.

Before joining Evidera, Dr. Rubino worked in the consultancy sector on complex drug safety studies and overall safety strategies for risk management purposes. From 2010 to 2015 Dr. Rubino was a Scientific Administrator at the European Medicines Agency (EMA), leading the development of guidelines on therapeutic risk minimization. In her earlier academic career, she was a Principle Investigator at the University College London (UK), where she was awarded several prestigious fellowships and grants.

Dr. Rubino has published more than 50 peer-reviewed articles, including papers on high impact journals (e.g., *BMJ, Trends in Pharmacological Sciences)*, and is an experienced speaker at international conferences. She holds a PhD in pharmacology from the University of Florence (Italy) and a master's degree in epidemiology from the London School of Hygiene and Tropical Medicine, London (UK).

Samantha K. Sites, MPH, CPH, is an Epidemiologist at Evidera, moving from PPD to Evidera's Real-World Evidence team and is located in the Raleigh-Durham area of North Carolina. Ms. Sites offers epidemiological and statistical support on a variety of risk management projects, observational research studies, and time-and-motion studies.

During her years as a graduate student, Ms. Sites worked as a research assistant in the department of epidemiology, where she focused on research analyzing the associations of childhood obesity, lifestyle factors, and breast cancer. Additionally, she was employed as a teaching assistant and had the opportunity to assist younger students while instructing two of the epidemiology department's core courses. Later, while interning at the U.S. Department of Veterans Affairs, Ms. Sites researched factors associated with depression among caregivers of stroke patients.

Ms. Sites earned her master of public health degree in epidemiology from the University of Florida. She also attended the University of Florida while completing her bachelor of science degree in nutritional sciences. Ms. Sites also holds a Certified in Public Health certificate issued by the National Board of Public Health Examiners.

Paul Swinburn MRes, is the Staff Director (EU) and a Senior Research Scientist for Evidera's Outcome Research practice in London. He has worked in the outcomes consultancy environment for a decade having previously taught research methodology and statistics in academia. His current responsibilities include overseeing staff recruitment and development for European outcomes operations as well as contributing to scientific activities. Mr. Swinburn has a particular interest in health utility, patient preference, and ePRO studies amongst other areas.

Mr. Swinburn frequently serves as principal investigator on large research projects and provides input on the design and delivery of research specifically targeted to the needs of a variety of stakeholders in the pharmaceutical development process. He has an extensive publication list and has published in such journals as *British Journal of Cardiology, Quality of Life Research, Value in Health* and *Medical Economics*. In addition, he has presented his work at many conferences including the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and EuroQol group meetings.

Mr. Swinburn holds a master of research degree in design and evaluation of interaction systems from Lancaster University and a bachelor of science (Hons) degree in psychology first class from the University of Lincoln.

Kristin Veley, PharmD, MPH, is a Research Scientist and Director, REMS and Pregnancy Registries in Evidera's Real-World Evidence team where she serves as the scientific lead for REMS programs, pregnancy registries, and other related studies. She earned her PharmD from the University at Buffalo, Buffalo, New York, and her MPH, with a focus in epidemiology and biostatistics and a certificate in maternal and child health, from Johns Hopkins University, Baltimore, Maryland.

Prior to joining Evidera, Dr. Veley worked as an associate director and senior epidemiologist at PPD where her focus was the design and analysis of REMS surveys and pregnancy registries. Prior to that, she was employed as a pharmacoepidemiologist at a specialty CRO in Baltimore, Maryland, where she analyzed and synthesized epidemiologic data and was involved in the design of patient registries for rare diseases.

Dr. Veley is a licensed pharmacist in the state of New York and practiced in the retail setting for six years prior to her employment in the pharmaceutical industry. During the course of her education, she also worked as a research assistant at Johns Hopkins University, participated in international field work in Bangladesh, and trained as a pharmacist in a variety of care settings. Dr. Veley's experience extends across a broad range of therapeutic areas including infectious, chronic, and rare diseases. Her combined education in pharmacy and public health offer a unique perspective to pharmacoepidemiological research.

Erica Velthuis, PhD, is a Director Epidemiology (PPD) with the Real-World Evidence team at Evidera. Dr. Velthuis holds a PhD in health sciences and an MSc in clinical epidemiology. She has been a registered Epidemiologist B in the Netherlands since 1998.

Dr. Velthuis transferred to Evidera in 2017 after working in PPD's epidemiology team for five years. In this prior role she provided support to observational studies that included a European focus or required her safety and risk management expertise. Before joining PPD, she was a senior pharmacovigilance scientist at Genzyme Europe BV for more than three years, where she provided epidemiologic advice and plans for the detection, assessment, understanding, and prevention of safety risks, and had final responsibility for the epidemiological evaluation in risk management plans. She oversaw epidemiological activities outsourced to CROs as well as research done by external parties, and participated in the IMI project PROTECT (Pharmaco-Epidemiological Research on Outcomes of Therapeutics by a European Consortium) Work Program 2 (Framework for Pharmaco-Epidemiology Studies).

Dr. Velthuis has ten years' experience in pharmacoepidemiology from her time working at NV Organon's drug safety surveillance department. There she gained broad experience designing epidemiological studies, providing epidemiological support for risk management plans and PSUR's, answering questions from health authorities by writing position papers and literature reviews, and setting up an automated signal detection and evaluation program by using disproportionality analyses.

Sheila Weiss, PhD, FISPE, is a Senior Research Leader, Drug Safety, at Evidera. With 20 years of experience in Pharmacoepidemiology and Regulatory Sciences, Dr. Weiss has worked in all sectors - academic, government, and industry - within life sciences. At Evidera she works on epidemiology research, risk evaluation and management programs, and other safety-related projects as a principal investigator or advisor. Dr. Weiss also serves as a consultant, working with clients on complex safety issues, regulatory milestones, and overall safety strategies for drugs and other regulated medical products.

Prior to joining Evidera, Dr. Weiss was professor, and founding director of the Center for Drug Safety, at the University of Maryland Schools of Pharmacy and Medicine, and a Visiting Professor at Johns Hopkins University. She has published approximately 50 scientific papers and given over 100 presentations, and has worked as an advisor and/or employee at a number of federal agencies including the FDA, NIH, and VA.

Dr. Weiss has a doctorate degree in epidemiology from Johns Hopkins University and completed a postdoctoral fellowship in pharmacoepidemiology and regulatory sciences at the U.S. Food and Drug Administration. Dr. Weiss is a Fellow of the International Society of Pharmacoepidemiology.

Evidera Acknowledges Excellence with Senior Staff Promotions

Agnes Benedict, MSc, MA
Senior Research Leader and Executive Director, Center of Excellence for Health Economics

Chris Gardner, PhD
Director, Market Access Communications

Marzieh Golbaz, MS
Lead Data Engineer, Evalytica

Shien Guo, PhD, MHA
Senior Research Leader and Senior Director, Modeling and Simulation

Phillip Hunt, ScD, MS, CIH
Research Scientist, Real-World Evidence

Anuraag Kansal, PhD
Senior Research Leader and Director, Disease and Trial Simulation, Modeling and Simulation

Dimitra Lambrelli, PhD
Senior Research Scientist and Director, EU Database Analytics, Real-World Evidence

William Lenderking, PhD
Vice President, Outcomes Research

Brian Murphy, MS
Principal Data Analyst, Real-World Evidence

Lindsey Murray, PhD
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Jiat Ling Poon, PhD
Research Scientist, Outcomes Research

Mireia Raluy, MSc
Research Scientist and Director, RWE-Europe, Real-World Evidence

Julie Roiz, MSc
Senior Research Scientist and Senior Director, Modeling and Simulation

Anne Skalicky, MPH
Research Scientist, Outcomes Research

Sonja Sorensen, MPH
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Rebecca Speck, PhD, MPH
Research Scientist, Outcomes Research

Tommi Tervonen, PhD
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Alex Ward, PhD, MRPharmS
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Yingxin Xu, PharmD, PhD
Senior Research Scientist, Meta Research

We're Hiring!

Due to Evidera's exceptional growth trajectory, we are interested in hearing from experienced healthcare/life science consulting candidates with expertise at all levels in the following content areas: meta research, health economics, real-world evidence, modeling, clinical outcomes assessments, project leadership, client engagement, and pricing and reimbursement. We generally prefer candidates who are able to work in one of our office locations, however, we will consider all qualified candidates. If you don't see an appropriate opening posted at this time, please email your resume and a cover letter of interest to careers@evidera.com.

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