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FOCUS SECTION

REAL-WORLD EVIDENCE

CARROTS AND STICKS: THE CHANGING INCENTIVES FOR USE OF REAL-WORLD EVIDENCE

Interview with Rob Thwaites, Senior Director, Takeda; and Chair, ABPI Pharmaceutical Health Information Group

MAY 2016

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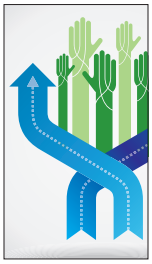

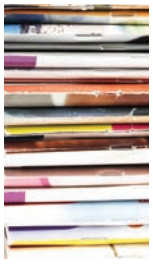

Time to Get Real about Real-World Data in HEOR and Epidemiological Research: Three Necessary Conditions for Better Data

Radek Wasiak, PhD
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Radek Wasiak

The Real-World Data (RWD) or Big Data revolution is upon us. From retail to engineering, from advertising to predicting travel patterns, we are subject to daily analysis of electronic pieces of information. In healthcare, much of the advance is happening in clinical research; linking genomics data to outcomes allowed us to go beyond a mere correlation analysis towards causality discussions in discovering why some are more prone than others to face certain health conditions.

Yet, the field of epidemiology and health economics and outcomes research (HEOR) is still struggling to fully grasp the possibilities. RWD are fragmented – they include only a sector of healthcare or are geographically constrained. RWD are incomplete – key outcomes are missing or are not routinely collected, and time stamps for major health events are not present or are subject to reporting bias. Access to RWD is restricted – many data owners do not allow external access to their data. Generating real-world evidence to support new product launches for present-day indications has become a challenge.

"It is the collaboration of multiple stakeholders involved in real-world evidence generation that is the first of the necessary conditions for improved RWD."

Many of these constraints are inherent to how the real-world evidence support system has developed; barriers were created and insufficient facilitators established. Reliance on existing data collection methods (claims data or electronic health records), confidentiality protection or data ownership laws, and the rules of research funding all contributed to the current situation yet are completely understandable given the history of the field and investment needed to generate patient-level information in a longitudinal way.

Are we therefore stuck with the imperfect system? Not necessarily, as there is a growing recognition that improvement is needed. Innovative Medicines Initiative's (IMI) GetReal is one of the initiatives recognizing the need to do better.[1] It aims to show how robust new methods of RWD collection and synthesis could be developed and considered for adoption earlier in pharmaceutical research and development and the healthcare decision

making process. (For more in-depth description of IMI GetReal goals, please read the interview with Rob Thwaites in this issue of *the Evidence Forum*). It is the ***collaboration*** of multiple stakeholders involved in real-world evidence generation that is the first of the necessary conditions for improved RWD. Development of standards, making more complex and robust approaches part of research standards, and ensuring comparability of findings through the use of tools such a common data model should be the desired outcomes of this increased collaboration.

The second necessary condition is an extension of the first one – real-world evidence needs to produce ***stakeholder-relevant***, and in particular ***clinically-relevant, outputs***. The drug development process has become increasing multidisciplinary, and issues related to market access and HEOR supporting market access are now discussed early as part of multifunctional brand teams. This increased visibility, which involves real-world evidence generation, requires going beyond technical delivery. For instance, RWE translational research should help clinicians understand what to expect from RWD studies, what constitutes good research practices, and how clinicians can get engaged in the design and interpretation of these studies; all these activities would only improve the value of investment in generated evidence. This would also help overcome the stigma of observational research as being lower in the hierarchy of scientific evidence than randomized clinical trials.

Finally, we need ***faster research outputs.*** In many cases, it takes more than a year to get access to data from the most recent calendar year. Examples are plentiful of the negative impact this has on research quality and impact.

"Real-world evidence has the potential power to change the way drug development works..."

Analyses of real-world treatment patterns or outcomes are outdated by the time they are made public. Post-authorization safety studies, focused on confirming that the drug is safe in actual clinical practice, are prone not only to challenges associated with a new drug gaining the necessary market share but also with data availability delays, causing them to run for several additional years. This extends beyond studies involving existing data sources; data collection studies do not produce results for several years, with frequent interim analyses often being cost prohibitive for the study sponsor. Many of these challenges cannot be easily overcome and will require non-research solutions, but there are some steps that researchers can take, in particular an increase in the use of technology and automation to speed up data management and analysis.

Real-world evidence has the potential power to change the way drug development works – adaptive licensing is one area where the need to use RWD early is essential. By focusing on collaboration among stakeholders and the importance of clinically-relevant and faster outputs, the healthcare industry can revolutionize the way we view real-world evidence and open up new, life changing, and even life-saving, treatments for improved health outcomes on a global scale. Barriers are meant to be broken.

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Carrots and Sticks: The Changing Incentives for Use of Real-World Evidence

Interview with Rob Thwaites

Senior Director, Takeda
Chair, ABPI Pharmaceutical Health Information Group

Rob Thwaites

Rob Thwaites, MA, MCom, is Senior Director at Takeda and one of the leaders of the IMI GetReal Project (www.imi-getreal.eu). GetReal aims to show how robust new methods of real-world evidence (RWE) collection and synthesis could be adopted earlier in pharmaceutical R&D and healthcare decision making processes. As co-project leader for Work Package 1, Rob has collaborated with a wide range of stakeholders in medicines development to assess the acceptability and usefulness of approaches to the use of RWE in assessing the effectiveness of new medicines. Rob has over 20 years' experience in healthcare, working for both industry and consultancies, and has worked in the UK, the U.S., and Australia. Rob holds degrees in Economics from the University of Cambridge and the University of New South Wales.

This interview was conducted by Radek Wasiak, PhD, Vice President and General Manager, Real-World Evidence and Meta Research, Evidera.

Three key features of real-world evidence are emerging: increased collaboration, need for stakeholder-relevant outputs, and increased speed of getting results. Regarding the first of these, there appears to be substantial fragmentation in RWE. IMI's GetReal is a great example of a collaboration effort bringing people together to address these issues.

Yes, that is the hope. People often are using the same data but for different decisions, so there is not only fragmentation of research, but also fragmentation of aims and of attitudes as well. In the work I have done on the IMI GetReal project, there has been a lot of feedback that this has been a great opportunity for us to work together with others in the healthcare sector and there is a true collaboration amongst people trying to tackle the same set of problems. I have seen good working relationships built, and real trust.

It is encouraging to hear. However, it does seem that new developments often take a long time to reach payers and health technology assessment (HTA) agencies, and consequently, real-world evidence and real-world data are still under-utilized, as many novel approaches are not well publicized.

Well, the information is available, but as you know in this field, people are often working with their own tried and tested methods in mind. For example, on the industry side, everything is focused around project teams and there is pressure to attain project goals, whether that is a drug in development or a drug already on the market, and if more novel approaches appear riskier than these well-established, though logical approaches, there can be resistance.

With the "hot topic" continuing to be big data or real-world data, CEOs and other pharmaceutical industry leaders are paying attention to RWE — a stark difference from a few years ago. This often resulted in the creation of RWE-focused teams. What has changed and what was the impetus?

The concept is not new but real-world evidence is still the "buzz word." Pharmaceutical companies have always used real-world evidence and real-world data, for example, to track safety once a drug hits the market. What is new is the extent of the data and the recognition that it can be used in so many different ways.

There are a number of factors driving it on the supply side, including the increasing availability of electronic, patient-level data for research, advances in methods, and the ability to link data sets. On the demand side, there is a much greater recognition among decision makers and their advisors that we have to complement clinical evidence with real-world evidence. We have seen this in the proliferation of HTA agencies and the increasing sophistication of advisors, formulary bodies, and HTA bodies. On the demand side, then, there has been huge growth in the need for this real-world evidence data and the recognition that this data has a role to play in decision making. So, because there is attention on both the supply and demand sides, there is now a stronger push for discussion and for collaboration among those who create and use the evidence.

Is it safe to say that RWE was "nice to have", at times mandated, but something that researchers "dabbled in" to help demonstrate product value, and now commercial and marketing teams actually need these data for market access and pricing and reimbursement purposes?

I think in the early years, companies did dabble a bit; if you go back to the formation of the first pharmacoeconomics departments in companies in the late `80s and early `90s, there wasn't really a great demand for this type of data from agencies that needed it for formal assessments. It is only once it started with the agencies, such as in Australia in 1992, where the requirement for evidence was introduced as part of a much bigger package to encourage investment in R&D in that country, that companies really started to invest in RWE.

I think you touched on a few things already, but thinking specifically of real-world data, what do you see as the key barriers to greater adoption of this type of evidence? And what would you see as facilitators to overcome those barriers?

I think there are barriers at different stages. There are challenges in terms of creating and accessing the data, and then again in synthesizing that data. After that, there is also a challenge in making sure the resulting evidence is used in decision making. I think some of the biggest barriers at the moment are more around the availability and the quality of the data. Secondly, there are barriers around the agencies' willingness to accept the data. There are some agencies that are quite open-minded about real-world data and are willing to live with imperfect data – data where there is uncertainty, and they are willing to try and understand it. NICE, for example, is constantly pushing to find ways of looking at different methods and different techniques whereby real-world data can be used. On the other hand, we have seen some agencies, in Germany, for example, where clinical trial data are still at the center of evaluations.

Going back to the issue of the content of the data, would you say that the easily available data are fit for purpose?

The measure of whether these data are helpful is whether the evidence from them is influential in decision making. If it helps people in healthcare, whether they be physicians, agencies, or even patients, make decisions, and hopefully better decisions, then that is really the measure of whether the data are getting to be good enough. We know there are pockets of data that are very good and are used often and routinely. For example, primary care data in the UK, claims data in the U.S., and registry data in the Nordics – there are a lot of good data sources. Where there's a gap in the data is when we have to resort to reverting back to clinical data alone. But even then, you still have to extrapolate and think about to what extent the data – whether it is clinical or real-world data in other settings – is transferrable to your specific setting. There are still questions about what methods of simulation or synthesis are going to be acceptable, for example. A lot of progress has been made, with acceptable approaches in that area by many decision

makers for over 20 years now. It is important to note, however, that these discussions are not just about the generation of new evidence, but also about simulation from existing evidence, how evidence is synthesized to ensure it is transferrable, or that the implications are transferrable from one setting to another.

You mentioned advances in methods. It seems that industry's willingness to accept more novel solutions and approaches is still limited. Do you see a way forward that is leading to some of the novel but highly relevant RWE approaches becoming standard and accepted by payers?

It is an interesting question about the acceptability of data and new approaches and the unwillingness within industry to push on that front. That is why collaborative efforts, such as IMI GetReal or other projects, are good because they do force different groups (academics, decision makers, suppliers, etc.) to work together to evaluate the acceptability of approaches to providing evidence. I think these collaborative efforts can be influential in pushing companies to think about other ways of generating evidence and forcing a dialogue between companies and decision makers.

Do you foresee any policy trends that would actually help with these earlier discussions?

We have to think about how we satisfy decision makers' demands for data and get patients access to medicines earlier, and that means providing evidence earlier in the decision making process. For example, if you wanted to get effectiveness evidence prior to approval, you could either set up a real-world study prior to approval, which is very unusual, or you could find ways of trying to model effectiveness from the efficacy data that you get. These are complementary, but really it comes down to the decision makers, the HTA bodies in particular, who will insist on use of real-world data as well as modeling. Modeling alone is no longer the answer because decision makers also want evidence of what is going on in real-world clinical practice.

One of the challenges with well-designed, real-world studies is that they can be quite expensive, yet there is a belief that the data are easily available and can produce results quickly. How can we overcome this perception?

The cost of research is definitely underestimated, and this is where education is so important. It is incumbent upon leaders and collaborative groups undertaking policy around these studies to clarify the processes and costs, but also the benefits associated with this investment. The assumption is that the data are there and easily accessed and synthesized, when in reality, the data are fragmented and often not clean, and every study is a bespoke study. As long as that is the case, the research is going to come with a higher cost. However, this research is still going to be cheaper than experimental or prospective research, for example. I also expect the cost of research will eventually decrease over time as we get better data, better knowledge, and more efficient research centers.

Another challenge I see is access to data, particularly in Europe where privacy laws are more stringent. Will this issue continue to play a role in the use of real-world data?

The question of access to data is a big issue in some countries, and yes, specifically in Europe. There has been an ongoing discussion at a European level about data protection and regulation over the last couple of years, and the proposed regulations were looking very unfavorable for research. From the UK, the ABPI, Wellcome Trust, and medical charities all responded quite strongly to those proposed regulations, and since the end of last year, there is a revised agreement between the European Commission and the Parliament council which looks more favorable for research. When implemented, that European model will then cascade down to individual countries, which will then have two years to implement the new regulations. Countries like the UK are quite positive about continued access to data for research purposes so that patients can get access to needed treatments, but the ethos in some other countries is quite different and I do see that as a big challenge for research in the future.

Where do you see sources like social media and data generated as part of activities of daily life (for example, personal device data) coming into play? Do you think these data are an unnecessary distraction right now, or should they be incorporated now as a part of the standard package of evidence? Safety, for example, is one area where use of social media is becoming more common and complementary of other adverse reporting mechanisms.

It's quite interesting, actually. We are used to working with clean data, and now with real-world data that may not be so clean but is still typically recorded by physicians or healthcare professionals. Now we have this spontaneously recorded information by the general public through social media, and it's a different type of data generated with a

different motivation. This is definitely an important trend, and I think we need to look at this data not as proof, but as indicators of what patients are experiencing or find relevant, for example, issues of safety or how treatments are being used. People in the industry will be looking at this data more and more, and it could prove to be quite helpful in understanding conditions and how these conditions affect patients. For example, what is important to patients with the disease, what issues they have with the condition, how they perceive their current treatment. I think there is a lot we can understand about unmet needs in the patient world, and I think we could do that now.

As we wrap up, let me ask where do you see this field in five years? If initiatives like the IMI GetReal are successful, what will be achieved?

I see two parts to that question. One is what is going to happen in the next four or five years. Secondly, where does the success lie? I think some of the trends that we are currently seeing will continue. Better data, better quality data, more linked data sets within countries, and some of the newer issues we just discussed will expand as well, such as social media and public data. We should be in a better situation in terms of data in general.

In terms of what we would like to see, we need to think about why we want access to this data, which is ultimately to advance and improve the quality of healthcare. I think the biggest single thing we will see in the foreseeable future is earlier access to new medicines. With so much activity in this area, such as the early access to medicine schemes (EAMS), the real-world initiatives such as Green Park in the U.S. and IMI GetReal in Europe, or the activities going on in individual countries, patients should hopefully be seeing earlier access to medications than they previously would have.

Is the true challenge then to bring it all together? Somehow to make sure the separate initiatives work together as an overall solution instead of seeing solutions vary between the U.S. and Europe, for example, or even worse, individual countries within Europe? Is that the biggest barrier to overcome?

I think your point about collaboration in the first place is a big barrier, yes. Changing cultures and the way people think about collaboration, acceptance of new evidence, and then implementation of that evidence into decision making – those are all needed to make a real change, but they are also extremely challenging. The efforts we are seeing now, for example, are a great first step in this process, but I would expect that external mandates requiring specific types of evidence at certain timepoints in the lifecyle process are probably what will be needed to truly see effective change. If, for example, all the major HTA agencies in Europe agree that certain evidence is needed, then there is obviously a better chance of consistency and acceptance.

We already see that some agencies, such as the EMA, mandate that drugs need to show evidence of safety in the real world. Some countries want data to prove that drugs are actually effective in the real world, and without that data, access or prices could be reduced. So, it may be that we don't see actual mandates for real-world evidence, but repercussions if that evidence is not provided. I think that is the only way development teams in industry will sit up and take these changes seriously. Otherwise, there will always be pushback from people within the industry, with concerns about the cost – and timelines – of studies that are not mandated, or that studies might show that their product's effectiveness is not as good as the efficacy shown in trials, or their product may not prove to be as good as the competition.

In the end, it is up to the agencies to set the requirements for this evidence.

It always comes back to incentives, doesn't it?

Yes. Carrots and sticks.

Carrots and sticks. That's a good way of finishing. Carrots and sticks.

Real-World Data Strategy: A Roadmap for Success

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The term "real-world data" is broadly applied and relates to diverse methodologies and approaches. Along the pathway to market access, data from outside of the clinical trial setting is considered a "must-have" to support compelling messages of product value, safety, and effectiveness. Regulatory bodies, like the National Institute for Health and Care Excellence (NICE) in the UK and the Institute for Quality and Efficiency in Health Care (IQWiG) in Germany have recognized that randomized controlled trials (RCTs), although the gold standard for assessments of efficacy, do not provide any information about drug effectiveness in the real-world care setting. Also noteworthy is the participation of NICE in a pan-European initiative to develop a uniform framework for the use of real-world evidence (RWE), the first results of which have been summarized in a recently published technical support document.[1] Other initiatives include the IMI GetReal[2], a consortium consisting of the European Medicines Agency (EMA), health technology assessment (HTA) bodies, academia, patient organizations, and pharma aiming to establish a framework to assess the relative effectiveness of medicinal products.

An International Society of Pharmacoeconomics and Outcomes Research (ISPOR) Real-World Task Force has defined real-world data quite simply as those data used for decision-making that are not collected in conventional RCTs and has identified six discrete sources.[3] (see Table 1.)

Additional sources of real-world data such as social media and cloud-based wearable health technologies add further to an already complex plethora of data available for life sciences research.

Evidence generation planning for successful market access must also include a multidimensional, real-world data strategy.

The early delineation of key value messages and associated evidence requirements, alongside a structured review of existing data gaps, are critical first steps for successful market access. This stepwise evidence generation planning process will serve to both identify and prioritize the research activities of importance – including the determination of real-world data needs. Questions related to *"which data"* from "*which sources*" and *"what methodology"* to address priority research objectives are at the core of a tailored fit for purpose data strategy.[4] The identification of optimal data sources and the robust derivation of meaningful outcomes, amidst the chaos of massive amounts of often fragmented snapshots of patient experiences accruing daily, can be a very complex exercise.

"The right data for the right research question" … the availability and suitability of each potential real-world data source must be thoroughly evaluated.

Real-world data can be obtained from existing sources or registries, including commercial data sources such as health insurance records, other administrative sources, or electronic medical records. The numerous existing sources of data can be either regional or restricted to specific healthcare facilities (e.g., specific hospitals), nationally representative, or even multinational. They differ not only in their content, but also the quality of

Table 1. ISPOR Task Force Sources of Real-World Data[3]

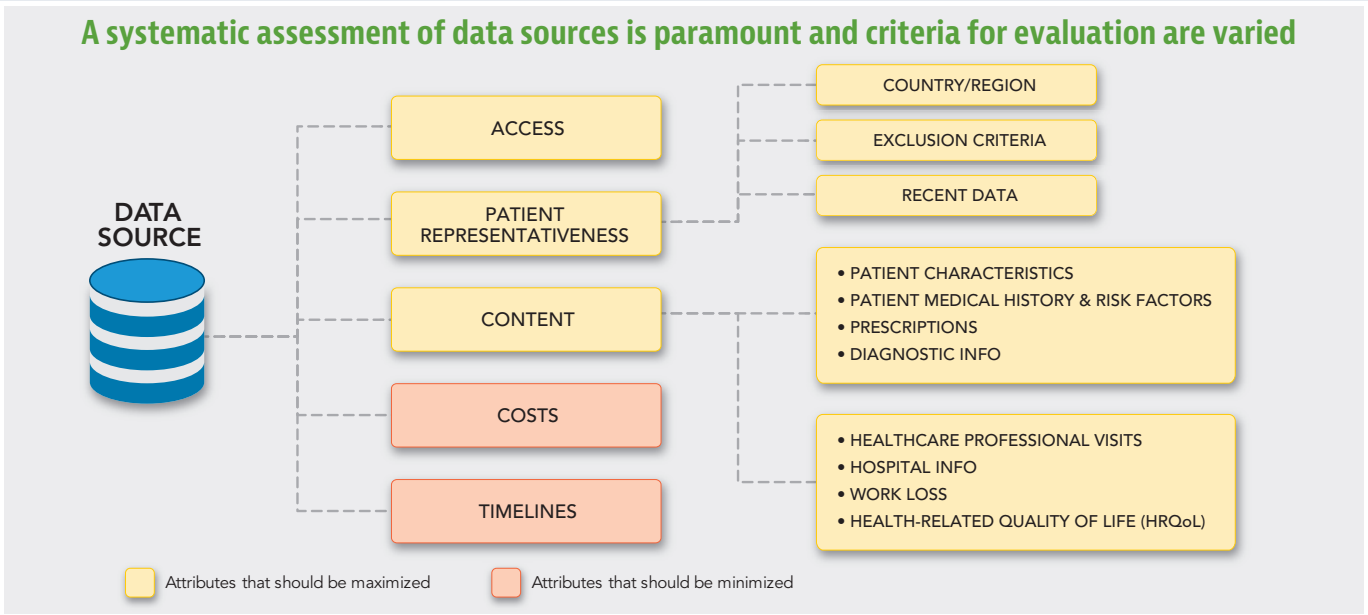
Source	Description
Supplements to traditional registration RCTs	Collection of data alongside clinically focused randomized controlled trials (RCTs); data include patient-reported outcomes (PROs), healthcare resource utilization, direct medical, and direct costs
Pragmatic clinical trials	Large trials that aim to measure effectiveness in routine clinical practice; the design reflects variations between patients that occur in real clinical practice
Registries	Prospective observational cohort studies of patients with a specific disease and/ or receiving a specific treatment involving prospective data collection
Administrative data	Retrospective data collected primarily for reimbursement but also contain diagnosis and procedure use and detailed information on charges
Health surveys	Designed to collect reports on health status and self-perceived well-being, healthcare utilization, treatment patterns, and healthcare expenditures from patients, caregivers, healthcare providers, or individuals in the general population
Electronic health records and medical chart reviews	Electronic data capture facilitates medical chart reviews (either prospective or retrospective) in the creation of datasets with longitudinal disease specific data at the patient level through data abstraction

the data, sample sizes covered, inclusion and exclusion criteria applied, and the settings of care that are being covered (hospital setting vs. outpatient setting). In addition, each of the data sources is ruled by its own terms and conditions that define data access that need to be taken into consideration when designing an RWE strategy, as these have great implications on the implementation timelines. Figure 1 summarizes the main criteria used to assess the availability and suitability of potential data sources.

Tailored de novo data collection studies can be designed to resolve data gaps, but structured feasibility assessments are paramount prior to study initiation.

In addition to a systematic appraisal of potentially suitable data sources, a thorough delineation of real-world data gaps and potential biases should be undertaken. In the context of multinational evidence generation activities, inevitably a mix of database analyses as well as de novo data collection studies across countries or regions will be required to achieve a robust

Figure 1. Overview of a systematic approach to database evaluation

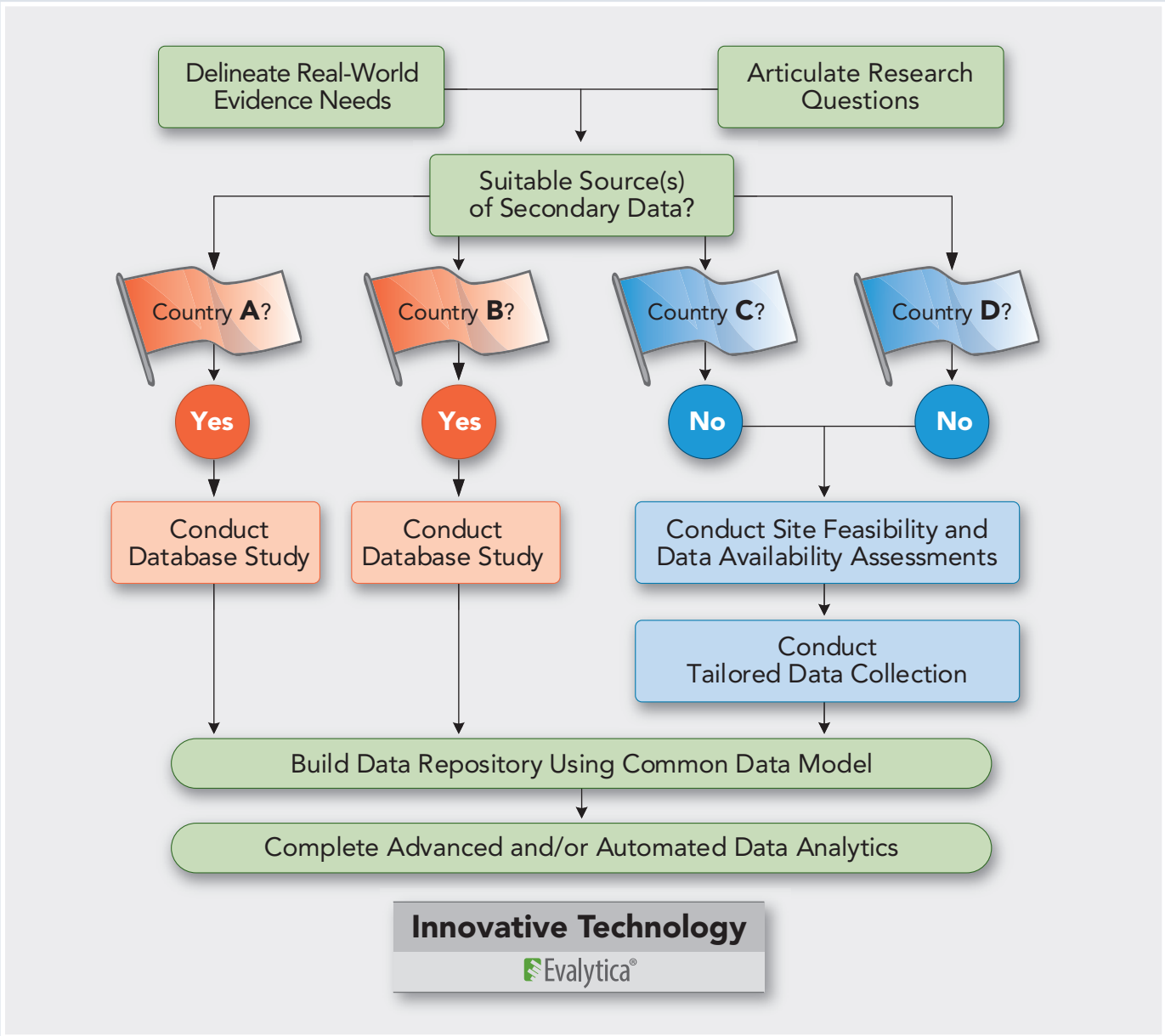


evidence base that has been adapted to the needs of each market.

Prior to the final design and initiation of any de novo data collection initiative, a comprehensive feasibility assessment at potentially eligible study sites is essential. A vital component of a thorough real-world data strategy, a carefully planned site feasibility assessment will serve to mitigate study risks as well as to inform project planning, including robust estimates of patient enrollment rates. Areas of key focus should include:

- Practice size and the existence of any mandated treatment pathways related to the therapeutic area of study
- Number of eligible patients by subgroup of interest treated per week or per month
- Medical chart management infrastructure and availability of key variables, if design incorporates medical chart review methodology
- Site institutional review board (IRB) and contracting processes, including unique requirements and timelines
- Availability of study staff for research conduct

Figure 2. A comprehensive real-world data strategy encompasses diverse methodologies and prioritizes technology and innovation



Data standardization and advanced or technology-enabled data analytics will ensure faster time to robust outputs and data interpretation.

A well-designed real-world data strategy can result in a multinational patient-level repository of real-world information that has accrued from a diversity of sources, including de novo data collection efforts. The utility of these custom repositories is greatly enhanced, however, when a common data model[5,6] that serves to standardize data vocabularies and formats is implemented. Standardization is highly recommended because it allows for the pooling and rapid analyses of highly variable and disparate data which inevitably result from programs of real-world research, as well as the following additional benefits[7]:

- improved efficiency, through reduced programming time,
- increased transparency as a result of "analytics democratization" and the opportunity to share coding algorithms,
- reproducibility of results across datasets, and
- "faster time to data" by leveraging automated data analytics tools, such as Evaytica.[8]

A comprehensive data strategy can provide a framework (see Figure 2) not only for the organization and prioritization of data sources and study types optimally suited to address the research questions of interest, but also to encourage various stakeholders within and across life science companies to plan for greater and more effective use of real-world data.

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Evaluating the Optimal Approach to Address the Research Question: What are the Trade-Offs Among Observational Study Designs?

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Teresa Wilcox

Observational data are often required to meet complex mandates by regulators and payers to demonstrate real-world product value, safety, and effectiveness. Guidelines on using real-world evidence exist[1], as well as questionnaires to assess the relevance (extent to which findings, if accurate, apply to the setting of interest to the decision maker) and credibility (extent to which the study findings accurately answer the study question) of observational studies.[2] These documents, as well as numerous Good Practice Task Force findings[3-6], set an expectation of scientific rigor and relevance. However, choices still exist in selecting the optimal approach to addressing the research question(s).

So many possibilities ... selecting the optimal approach

A number of study types can be executed that result in tailored, fit for purpose data to demonstrate real-world value of biopharmaceutical products and medical devices. These data may be used to demonstrate unmet need, populate and validate economic models, and aid in the development and implementation of PRO instruments. These can include literature-based meta-research techniques, database analytics, medical chart reviews, surveys, and prospective studies.

The selection process should be grounded in good research practices and consider the following:

- What are the key research questions?
- Who is the target audience for the findings?

"It is important to agree which research questions take priority if trade-offs are to be made in the study design."

- Who are the patients of interest and how best can you identify them?
- What are the design considerations associated with the research questions?
- What are the timeline and resource constraints?

What are the key research questions?

Often, researchers have a number of questions they are interested in addressing with an observational study and the list tends to grow as the excitement for the project expands among internal stakeholders. Teams are very interested in understanding the target population, unmet need, patient journey, treatment outcomes, and the potential role or impact for a product or disease area. It is important to agree which research questions take priority if trade-offs are to be made in the study design. Additionally, it is important to have well formulated questions to inform study design; ambiguous questions lead to a high risk of useless findings. Study design choice is highly influenced by the breadth and granularity of the essential elements of the research questions.

Cohort characterization

Characterizing the cohort of interest can have a number of components. One might be interested in the incidence and/or prevalence of the disease of interest, which can heighten the importance for understanding the underlying general population (i.e., the equation denominator) and new cases of the disease. Also, the target cohort may be such that it is important to describe their sociodemographic and clinical characteristics so that decision makers can readily identify the patients in routine clinical practice and/or within their health system. Lastly, identification of key risk factors for disease

progression, treatment failure, or an adverse outcome may be critical in supporting a value proposition for early intervention or use of an alternative treatment option.

Unmet need

Central to most product value propositions is residual unmet need in the target population – either to the patient, caregiver, and/or health system. The research questions relate to the impact of the disease on the patient's underlying physiology, severity of signs and symptoms, clinical sequelae, functional status, and health-related quality of life. Depending on the perspective of the target audience, these questions can extend to assessing the associated impact on the caregiver, health system, or society. Often, this incorporates evaluating the effect, lack of effect, or risks of current standard of care.

Patient journey

Understanding the patient journey provides insight into the diagnostic and care pathway, timing of disease progression, and current treatment patterns. While sponsors may have an initial map of the journey from advisory boards or market research, data from observational studies may be vital for quantifying or monetizing the journey for burden of disease messages or to inform and provide data for economic models. Findings can be used to evaluate opportunities for improving patient care by changing the evaluation process or offering new and/or early intervention into the course of the disease. Design considerations include the breadth and heterogeneity of sites of care, providers, diagnostic and treatment options, and health system differences.

Treatment outcomes

Assessment of treatment outcomes via observational research frequently includes evaluation of current treatment options. This might include clinical effectiveness, safety, and/or treatment adherence as it is well recognized that while randomized clinical trials (RCTs) provide strong internal validity, they are limited by their generalizability to the "real world." Thus "real-world" evaluation of treatment outcomes may focus on diversity of the patient population, indications for use, long-term outcomes (both effectiveness and safety), and the influence of provider and patient behavior. In some instances, the essential purpose is to bridge between clinical trials of the new intervention and clinical practice; either because comparative assessment requires data for a particular measure that was not collected in the RCTs for the current standard of care, or because an essential study measure is not routinely assessed in clinical practice.

Economic impact

For any of the above elements (cohort characterization, unmet need, patient journey, treatment outcomes), description of the impact on the patient, health system or societal resources can be important. This can be reported as units of use (days lost from work, emergency

Case Study 1: Evaluating an established cohort from the payer perspective

Situation: *The sponsor is interested in four research questions in descending priority.*

1) What are the treatment patterns following diagnosis (well-defined by ICD-10 codes) for the subsequent year?

2) How often do patients switch treatments and what are the reasons for switching?

3) What is the time-to-disease progression as measured by a change in radiography?

4) What is the current prevalence of this cohort?

Topic	Administrative Database	Chart Review	Patient Survey	Longitudinal Observational
Treatment Pattern	***	**	*	***
Switching/Reason	*	**	**	***
Time-to-Disease Progression	*	**	*	***
Prevalence	***	*	**	**

* fair ** good *** excellent

Design consideration: *Bearing in mind the target audience being a payer, one might consider a chart review or longitudinal observational study design. However, mitigating circumstances such as the timeline until data are required or available budget might alter this choice.*

department visits, etc.) or as monetary costs. This is one area where it is particularly important to understand the granularity of detail required. For example, is it sufficient to report that an adverse event occurred, or is it critical to describe the specific procedures and associated resources for that event?

Who is the target audience for the findings?

Understanding the level of precision and robustness for the findings required by the target audience offers guidance on the design, endpoint selection, and cohort source. For example, in selecting a source cohort, if the study's target audience is a clinical development team that is finalizing a comparator arm for a randomized trial, broad representation of clinical practice is critical, while if the goal is to gain a detailed understanding of caregiver impact for a particular subgroup, a more targeted approach might be taken to identify the source cohort.

Internal intelligence

Questions asked by internal stakeholders such as portfolio planning, clinical development, and pricing might include 1) characterization of target populations; 2) description of the current treatment patterns, including order of treatment progression and use of combinations; 3) benchmarks of concurrent comorbidities, complications, and outcomes of care; and, 4) residual unmet need where a new option might be positioned.

External decision maker

Study design and source cohorts can vary widely among research for external decision makers (patients, providers, regulators, and payers) as each applies unique decision making criteria on availability, selection, and use of an intervention. For example, while payers and patients are interested in quality and cost, the measures of quality and the source of costs differ for each group. U.S. payers assess quality of chronic obstructive pulmonary disease (COPD) care by the presence of a spirometry assessment, while patients are interested in relief of symptoms and the ability to perform daily activities.

Who are the patients of interest and how best can you identify them?

Identification of the source cohort (or sampling framework) for a study is critical not only to the structure of study operations but also to the precision and robustness of the findings. Research questions which impact the selection of the sampling frame might include:

- What are the clinical characteristics of the target population? If, for example, the condition is rare or a product has a low market share, one might consider site based design (chart review, prospective observation) where one could gather granular data on the target population.
- How large are specific subgroups? One would need to consider a design which allows collection of data across a broader cohort where the subgroups exist. Challenges could exist if histological examinations or laboratory test results are needed that might not be available in an administrative database.
- Who are the treating clinicians? The source cohort for the study must include these prescribers. For example, using a general practitioner data source would not allow one to track chemotherapy patterns that must be followed by an oncologist.

What are the design considerations?

A number of additional challenges must be considered in designing a study.

Representativeness

If there is a priority to represent the target population, one must consider the approach to sample ascertainment. Consideration should be given to a source cohort that is similar to the population it represents, or in some cases consideration should be given to conducting the study in multiple source cohorts. For example, when it is known that there are differences in care and potentially outcomes based on health system/country differences.

Need for long-term follow-up

If long-term follow-up is critical, source cohorts either have the ability to track the participants continually over time, possibly independent of provider/payer, or have the ability to collect data intermittently without significant loss to follow-up.

Alignment to Clinical Trial Findings

While measurement of clinical practice endpoints in a randomized clinical trial allows for easier interpretation of study findings, this is not always possible. A real-world study may be designed to provide a bridge between the clinical trial results and longer term clinical outcomes (e.g., bridging between QTc interval length and the risk of sudden cardiac death).

Precision of the Estimate

While one can estimate the precision of an estimate with a specific degree of confidence (e.g., 95% confidence interval), there are a number of factors which can affect this. For example, there can be systematic bias in missing data, measurement error, specification error, etc.

To address these challenges, a hybrid design as Case Study 2 may be necessary.

Case Study 2: Hybrid design to address breadth of sample and granularity of endpoints

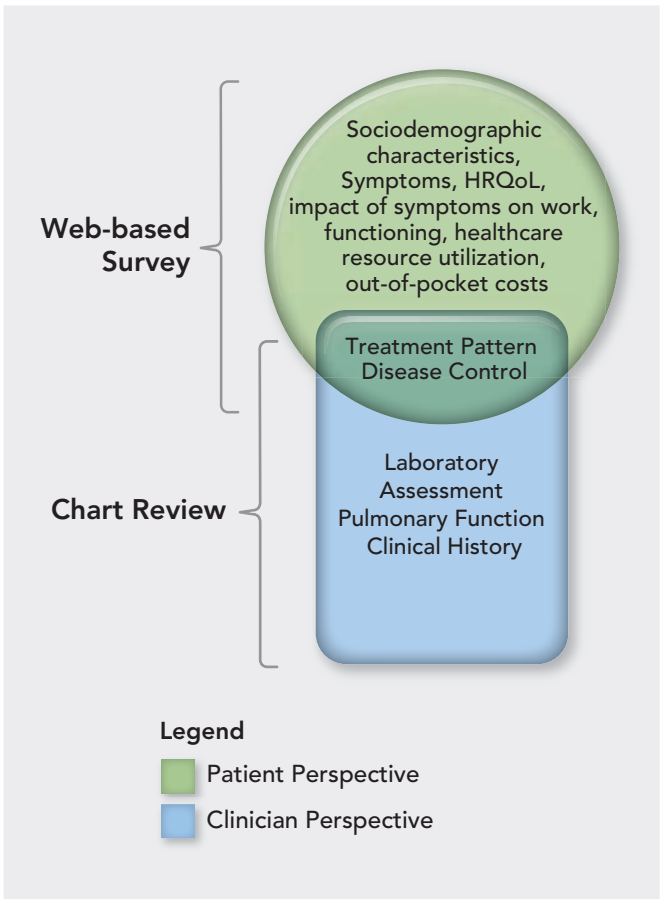
Situation: *The sponsor was interested in two key research questions with equal importance.*

1) What is the prevalence of the target population?

2) What is the disease burden and unmet need in the target population?

Measure of poorly controlled symptoms in the present maintenance treatment is indicative of a need to change therapy. However, among those with poorly controlled symptoms, the new product only treats those with an elevation of a specific serum marker and it is anticipated this is a small subgroup of the overall population. Furthermore, the primary endpoint in the clinical trial is measurement of pulmonary function.

Design Considerations: *As both detailed clinical characterization of those with poorly controlled disease and the presence of the biomarker and understanding the patient perspective of burden are important, a hybrid design chart review and a web-based patient survey was implemented. The chart review allowed the study team to capture the clinical detail associated with relevant biomarkers and clinical assessments, while the web-based patient survey provided the opportunity to describe the unmet need and impact of a breadth of patients with poorly controlled disease. A bridge using treatment patterns and measure of disease control was used to bridge between the data collection vehicles.*



Case Study 3. Same cohort, different design choice based on balance of data requirements and time constraints

Situation: *Two study teams considered a similar set of study parameters and concluded that different designs were the preferred choice. The decision between the two designs was driven by the requirement for longitudinal data, clinical confirmation of disease parameters, and timeline for data availability to decision makers.*

Topic	Study 1	Study 2
Cohort	Any treatment status	Naïve to prophylaxis
Geography	Global	U.S. (plan for global)
Need for clinician diagnosis	Not important	Important
Primary question(s)	Characterization of Unmet need healthcare resource use (HRU), non-traditional care, QoL	Treatment specific experience
Timelines	<12 months	18-24 months
Decision	Web-based patient survey	Longitudinal site-based with patient survey with clinical evaluation

What are the timeline and resource constraints for this project?

While in an ideal world all study design and implementation decisions are driven by scientific rigor balancing internal and external validity, this is not the reality for most study sponsors. The timeline for data generation and interpretation to meet decision maker requirements can be short or there are resource constraints within the sponsoring organization. Thus the selected study design is based on an assessment of the possible approaches to consider the trade-offs between the interpretation/bias of the findings and available time and resources. Even with similar research questions and similar target populations, different choices can be made, as seen in Case Study 3.

Conclusion

While to the untrained observer, collection of real-world evidence may seem "easier" than collecting data for a randomized clinical trial, I would suggest that the challenges are not easier; they are different. It is important to consider the breadth and importance of the research questions, the target audience for the findings, the target population being studied, as well as a number of other design challenges. Additionally, one must accept that there is rarely one perfect design which addresses all of these factors – let alone accounts for time and resource constraints. Regardless of the choice, good research practices for collecting and reporting real-world data are required. **The informed choice is yours!**

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The Future of Real-World Evidence Technology: Moving beyond "Rapid Cycle Analytics"

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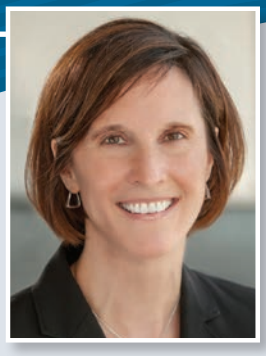

Stephanie Reisinger

Overview

Over the past several years a new breed of real-world evidence (RWE) analytic platforms has emerged, enabling researchers to submit analysis parameters through a user-friendly interface, execute modular analytic programs across a variety of data sources, and produce results rapidly without custom programming. These RWE platforms emphasize shortened analysis cycle times, generating results in minutes or hours for analyses that used to take days, weeks, or longer. There is no denying that these *rapid cycle analytic* platforms have had a meaningful impact on analytic efficiency. However, many are proprietary – forcing RWE organizations to choose a single technology solution, or manually mediate workflows and analysis results across multiple solutions. As these platforms increase in number and availability, they also contribute to an increasingly fragmented and disorganized RWE environment.

At the same time, a significant body of research highlights the benefits of data standardization as a way to help manage issues caused by the growing volume and heterogeneity of real-world data. A standards-based ecosystem supports interoperability among diverse RWE stakeholders, enabling RWE analytic platforms that "plug into" the standard to deliver not only analytic efficiency, but also reuse and reproducibility. The greatest benefits of data standardization will only be achieved with the adoption and use of a single standard across an entire RWE ecosystem, and those benefits are substantial. Use of a single standard extends the capabilities of RWE analytic platforms beyond the current focus of rapid cycle analytics towards an environment of true analytic democratization.

"The greatest benefits of data standardization will only be achieved with the adoption and use of a single standard across an entire RWE ecosystem, and those benefits are substantial."

The Current RWE Environment: Fragmented and Rapidly Evolving

The growing need for evidence generated from real-world data is disrupting the product development lifecycle. Real-world evidence is essential at every stage – from understanding product value and achieving favorable market access, to preserving and enhancing product positioning. At the same time, the RWE environment is evolving rapidly. Several current trends have the potential to significantly impact the way in which evidence is generated in the future.

Data, Data, and More Data

While secondary analysis of health system data has been used in epidemiological research for decades[1],

the volume and variety of secondary data available for real-world evidence generation is exploding, both in the U.S. and across the globe. In the U.S., the availability of patient electronic health record (EHR) data for medical research is expanding, partially catalyzed by the widespread implementation of "meaningful use" standards that provide incentives for providers and hospitals when they use EHRs to achieve specified improvements in care delivery.[2] Unlike many other secondary data sources, EHR data sources provide patient data collected at the point of care in near real time, blurring the boundary between retrospective and prospective research. In addition, many EHR systems also include previously untapped sources of real-world data, such as free-form text found in physician notes and imaging data in therapeutic areas where images are used in diagnosis and treatment.

Beyond health systems, data generated by individuals – mobile health data and social media, for example – are growing exponentially. Consider the following:

- Individuals generate 70 percent of all available data worldwide. More data has been created in the past two years than in the entire previous history of the human race.
- Within five years there will be over 50 billion smart connected devices in the world, all developed to collect, analyze and share data.
- By the year 2020, about 1.7 megabytes of new information will be created every second for every human being on the planet. Our accumulated digital universe of data will grow from 4.4 zettabytes today to an estimated 44 zettabytes in 2020.[3]

Yet, less than 0.5 percent of data currently generated by individuals are analyzed or used today.

A Patchwork of Analytic Capabilities

There are a growing number of both commercially available and internally developed RWE analytic platforms, providing a wide variety of analytic capabilities. For instance, many data providers include "query tools" to analyze their own proprietary data. Some analytic platforms target a specific type of analysis (e.g., pharmacovigilance), while others focus on analysis of a particular type of data (e.g., observational data, social media) or a specialized technical issue (e.g., natural language processing, data visualization). Overall, these RWE analytic platforms have had a significant, positive impact on the speed and efficiency of analysis execution. However, many also include proprietary technologies, methods, and/or data, forcing RWE organizations to manually address gaps, overlaps, and inconsistent workflows among platforms, and to mediate conflicting sources of evidentiary "truth" when different analytic platforms produce conflicting results.

Evidence Generation as a "Shared Service"

Until recently, real-world evidence generation has mainly been a specialized function – confined to teams with custom resources, data, and technologies to address the specific evidence generation needs of that team. However, this silo mentality is beginning to change as enterprises recognize that the same real-world data, technologies, and resources can support evidence generation needs across an entire organization. RWE Shared Service Centers are growing in popularity, providing centralized evidence generation capabilities across a broad and diverse population of evidence consumers. The main objective for providing evidence generation as a shared service is to increase efficiency and cost savings through the sharing and reuse of data, technology, resources, and analytic expertise.

Real-World Data Standards: Ready for Prime Time?

Standardized approaches to real-world data analysis have been widely studied as a means to cope with growing volume and heterogeneity of real-world data. Analysis standardization relies on the "harmonization" of the data – that is, the use of common words (data elements and terminology), structures, and data organization across disparate data sources. This is often accomplished through the use of a Common Data Model (CDM).[4]

Several research networks have developed and implemented CDMs into their clinical research infrastructure as a means to promote efficiency in evidence generation practices and to provide better interoperability among diverse research partners. These networks, briefly described below, provide a public forum for advancing the science of analysis standardization, while highlighting the benefits (and drawbacks) of such approaches.

- **The Observational Health Data Sciences and Informatics Program (OHDSI)**
  OHDSI (pronounced Odyssey) is a multi-stakeholder, open source collaborative with an established international network of researchers and observational health databases. OHDSI research is focused on the development standardized methods and tools for large-scale analytics of health data using the Observational Medical Outcomes Partnership (OMOP) CDM.[5,6]
- **The FDA Mini-Sentinel Program**
  Mini-Sentinel is a pilot project sponsored by the U.S. Food and Drug Administration (FDA) to create an active surveillance system to monitor the safety of

FDA-regulated medical products. Mini-Sentinel uses retrospective electronic healthcare data from multiple, distributed data partners, and has developed the Sentinel Common Data Model (SCDM) enabling collaborating institutions to quickly execute modular, distributed programs against partner data.[7]

- **The National Patient Centered Clinical Research Network (PCORnet)**
  PCORnet, an initiative of the Patient-Centered Outcomes Research Institute (PCORI), is designed to make it faster, easier, and less costly to conduct clinical research than is now possible by harnessing the power of large amounts of health data and patient partnerships. The PCORnet Common Data Model provides a streamlined, efficient way to use the data produced by these partnerships.[8]

- **The Innovation in Medical Evidence Development and Surveillance (IMEDS) Program**
  IMEDS is a public / private partnership offered by the Reagan-Udall Foundation of the FDA. IMEDS' primary objective is to advance the science and tools necessary to support post-market evidence generation on regulated products. IMEDS research includes both the SCDM and the OMOP CDM.[9]

Each of these research communities has produced compelling results that highlight the benefits of a CDM. However, despite a growing body of promising research and many similarities between available CDM standards, the implementation of different CDM standards can lead to different results in certain situations[10], leaving many RWE organizations unsure of how to proceed with data standardization.

The Future of Evidence Generation: Standards-Based, Efficient, and Democratized

As the need for real-world evidence intensifies, RWE organizations who are the most proficient in evidence generation will have a significant competitive advantage over their peers. However, these organizations are currently struggling with an explosion of disparate data and technologies, coupled with a lack of standards, all of which contribute to an increasingly fragmented and inefficient environment for evidence generation.

Data Standardization using a CDM has been widely studied as a way to enable agile research, providing a framework for rapid and transparent analyses across heterogeneous databases in support of research-related questions. Several research communities have developed CDMs for real-world data analysis; however, differences in these CDMs can lead to inconsistent analysis results. In order to fully realize the benefits of using a CDM beyond individual research communities, the adoption of a single, universal data standard will be necessary. This requires the convergence of existing CDM research into one uniform set of data standards that are accepted and implemented across diverse RWE researchers, communities, and stakeholders. While alignment of existing CDMs may be difficult to achieve, it provides the greatest potential for expanding CDM research and use beyond the boundaries of individual research communities into the broader RWE ecosystem. The main benefits of an industry-wide, uniform data standard are summarized below.

Interoperable and Reproducible

Adoption of an industry-wide data standard would provide an interoperable evidence-generation infrastructure supporting diverse organizations – researchers, RWE organizations, data and technology vendors, etc. Any analytic program or technology could "plug into" the standard and analyze any data source conforming to that same standard. Moreover, analysis results produced from a CDM are easily reproducible and meaningfully comparable across disparate data sources.

This is substantiated by the results of several studies. In one recent study, OHDSI researchers replicated an analysis across six disparate databases in the OMOP CDM format using one analytic routine, efficiently producing a consistent set of results. Without the CDM, independent programs would be required for each database and results may not have been directly comparable due to differences in the data structure, source vocabulary, and analytic module customization.[11]

Open, Transparent, and Collaborative

The use of a CDM facilitates standardization across the evidence generation lifecycle, making it possible for RWE stakeholders from diverse backgrounds (clinical, epidemiology, data science, technology, etc.) to work together. For instance, modular analysis programs written for CDM-format data can be developed and distributed for use across an organization. Parameters for selecting patient cohorts, healthcare events, and covariates can be defined and stored in a library for reuse and sharing. The industry-wide adoption of a common data standard also supports the creation of transparent, open source repositories of cohort and event definitions, and modular analysis programs. Interested stakeholders from across the entire industry could develop, publish, share, and reuse cohort and event definitions and analysis modules, moving away from a fragmented environment of custom analytic programs and technologies towards an environment of collaboration and analytic democratization.

Getting from Here to There

Rapid-cycle analytic technologies represent an important advance in the pursuit of improved evidence generation practices - but this is only the first step. A growing body of research substantiates the notion that adoption of data standards through the use of a CDM provides the foundation for an interoperable, transparent evidence generation ecosystem. Data standards not only support efficient evidence generation, but they also promote sharing, reuse, interoperability, and reproducibility across diverse RWE stakeholders. In this environment, data providers, technology providers, researchers, and other RWE stakeholders can continue to innovate and develop new analytic offerings, while increasing the value of those offerings by plugging into a standardized infrastructure that supports interoperability and integration with the rest of the RWE ecosystem.

There are a handful of similar CDM standards available today, each making a significant impact within a confined community of researchers and users. Convergence of these standards into a single, universal CDM could potentially spread the benefits of standardization beyond research communities and into the RWE ecosystem. Moreover, adoption of a uniform standard could facilitate better harmonization of the research being done by these communities. Future research could be directed towards extending the universal standard to include additional types and sources of real-world data such as images and free-form text as well as data created by individuals and prospectively captured real-world data.

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Optimizing Cost and Timeline Efficiencies in Late Phase Research

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Delineate Evidence Requirements

Evidence requirements to support the demonstration of safety, effectiveness, and value of a product now extend beyond market launch. Optimal product positioning and market uptake require a thoughtful multiyear, multidimensional strategy that culminates in an evidence base that will facilitate product coverage, reimbursement, and adoption. Value demonstration planning and strategic evidence gathering should ensure that available data are fully integrated and new research projects are designed to build on a unified body of evidence that will effectively communicate both the benefits and risks of a new medicine or technology. To achieve a comprehensive evidence base that meets the needs of a myriad of stakeholders, a broad array of scientifically robust national and international studies must be conceptualized, designed, and implemented within a relatively short period of time – typically no more than five to seven years. With research and development lifecycle costs of a single product estimated in the billions of dollars[1], evidence generation planning needs to be initiated as early as possible to ensure the right evidence is generated in the most cost-effective manner.[2]

Conceptualize Programs of Late Phase Studies Early

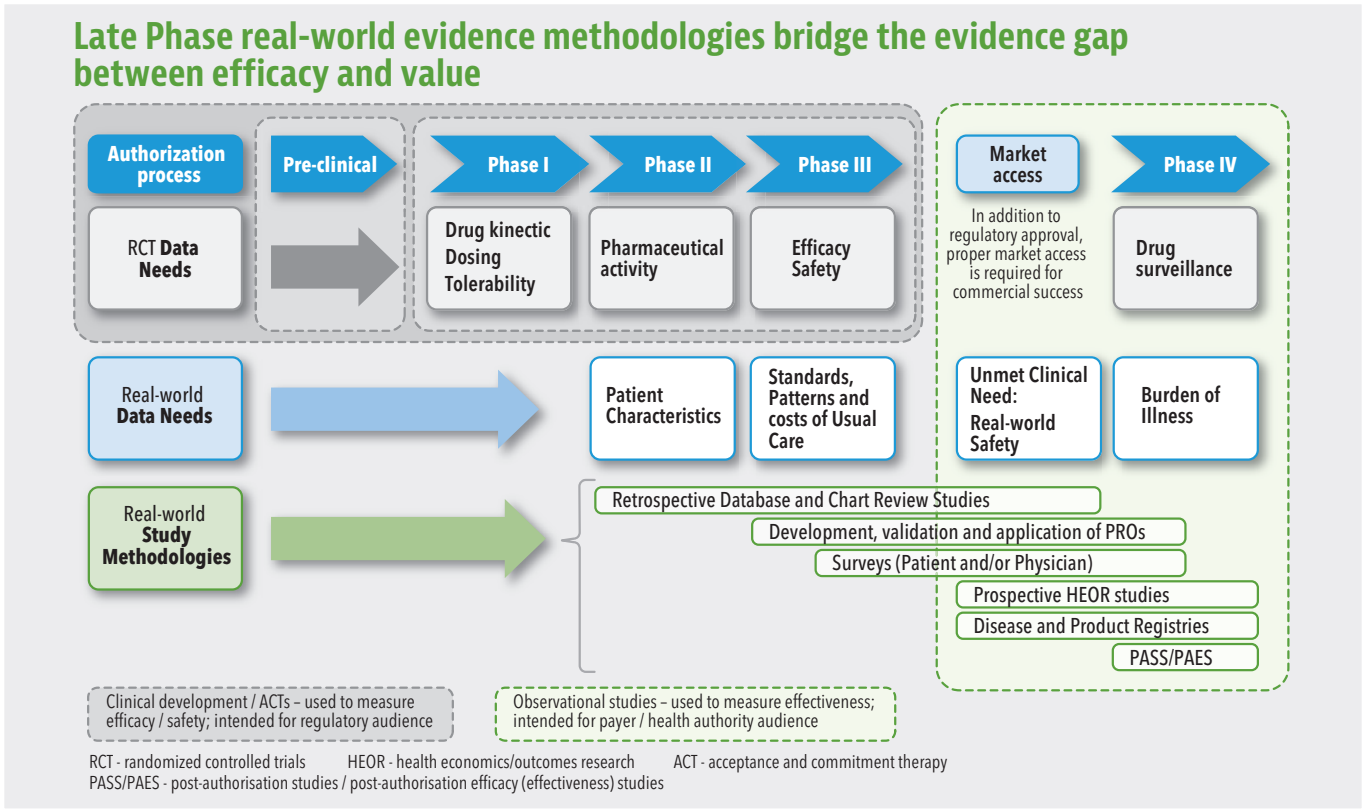
Fundamental to evidence generation planning and a real-world data strategy is a systematic evidence gap assessment and real-world data strategy. Once complete, methodologies for late phase evidence generation spanning analyses of secondary data sources, as well as de novo data collection needs, can be identified and prioritized – the latter associated with significant additional cost and timeline requirements. Even the simplest of protocol-driven, real-world data collection studies require significant time and investment, and costs increase further when compounded over multiple studies and years to support a full range of product safety, value, and effectiveness messages (see Figure 1).[3]

With the aim of optimizing cost and timeline efficiencies, multiyear research programs comprised of stepwise and synergistic de novo data collection studies should be conceptualized and executed. Unfortunately, given the sheer volume and diversity of data that are required to support multinational product launches, information silos, and organizational complexities within pharmaceutical and device companies, late phase studies are instead frequently designed and executed as separate stand-alone initiatives. These explanatory factors, as well as others, contribute from the outset to an inherent evidence gathering inefficiency that may require a paradigm shift in study planning if significant time and research dollars are to be saved.

Designs employed to gather real-world evidence vary markedly in terms of study parameters and scope, thus opportunities to incorporate efficiencies within a program of studies may not be immediately obvious. For example:

- Often considered retrospective registries, multi-national retrospective chart review studies can be used to build comprehensive patient-level repositories of international clinical and resource utilization data. These data can inform current patterns of treatment, including off-label prescribing, populate burden of illness, and other more traditional health economic evaluations, and inform trial or registry designs.

Figure 1. Real-world evidence (RWE) requirements span safety, effectiveness, and value



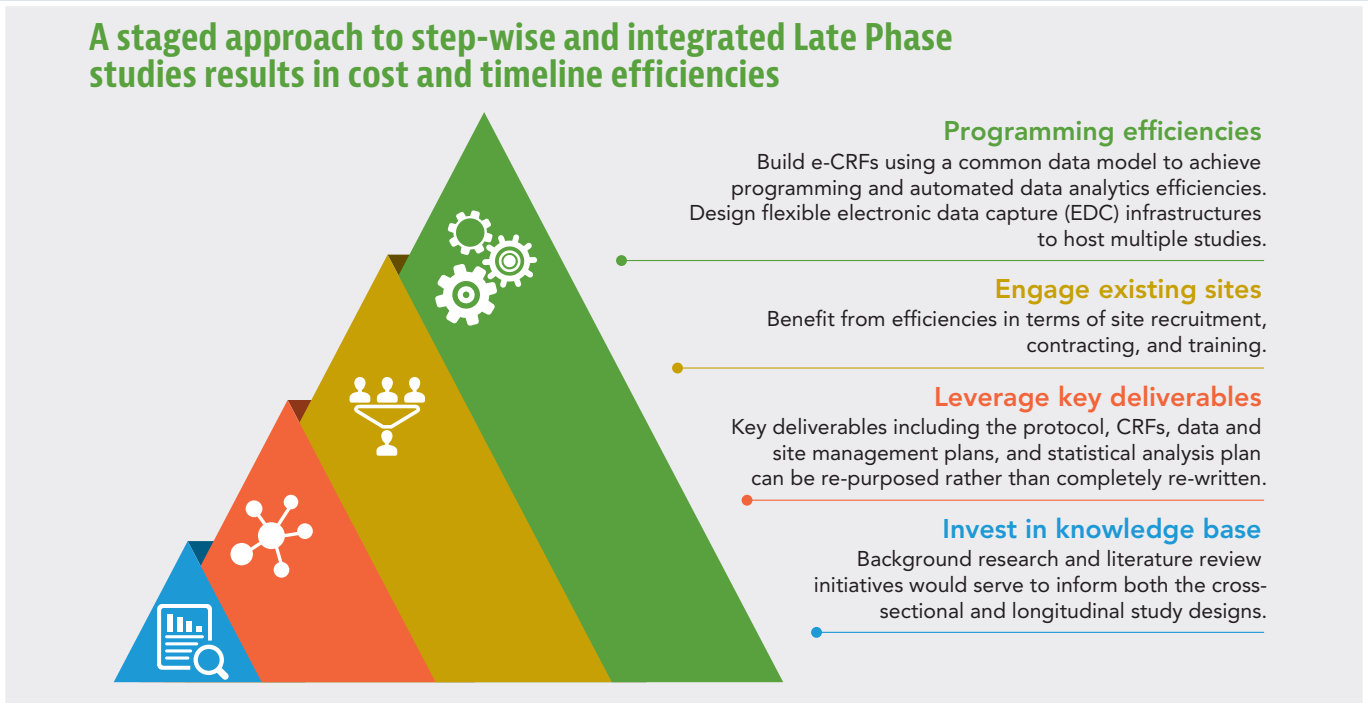
- Multifaceted prospective studies, including disease registries, are another important source of "benchmarking" data that also reflect natural history of disease and standards of care, but also include patient-reported outcomes (PROs) and other effectiveness outcomes. Pregnancy and product exposure registries are implemented to better understand real-world product safety and conditions of safe use.

- Pragmatic trials, which are observational in nature but with the added benefits of randomization, evaluate comparative effectiveness – increasingly important in the context of current trends in product commercialization and spending.[4]

Despite such differences in study aims, objectives, and specifications, important cost and timeline efficiencies can be realized by systematically seeking out and building upon methodological and operational synergies. Each of these study types aim to collect real-world patterns of care, and clinical, safety, and effectiveness outcomes. Because each of these studies would be executed as part of the same product's commercialization process, key design elements – including patient selection criteria, sub-groups of interest, clinical and patterns of care variables of interest, and other patient outcomes – are likely to overlap significantly. For example, though research questions may vary markedly, patient selection criteria, subgroups of interest, clinical and resource use variables, and other outcomes of interest are likely to be consistent. These synergies can be exploited both by "recycling" selected content from study documents, such as protocols, case report forms (CRFs), informed consent forms, statistical analysis plans, and even statistical programming code. If the number of study protocols can be reduced, so can the number of site contracts and ethics and other mandatory approvals, as well as the number of months of study start-up. While the efficient use and repurposing of study materials from one project to another over time is primarily a documentation, communication, and knowledge transfer exercise, combining study protocols to achieve hybrid, longitudinal designs requires a bold, strategic vision and multiyear commitment of resources. Those willing to make this level of upfront strategic investment do so with an inherent belief that over the product commercialization period, the total cost and resource requirements of the program as a whole will be significantly less than if each study was conducted as a standalone initiative (see Figure 2).

A schematic representation of a stepwise approach to the integration of multiple real-world studies, including a chart review, a prospective study, and a product registry over multiple years, is shown in Figure 3. Foundational chart review activities provide important information about variability in patterns of care and clinical outcomes, but they can also serve as the means to identify

Figure 2. Opportunities for synergies and efficiencies



prevalent cases of interest for enrollment in a prospective study such as a disease registry. Once implemented, prospective studies including disease registries, within which a wealth of clinical, health economic, and PRO endpoints can be collected, can also be a highly efficient framework to evaluate the real-world safety profiles of new and emerging products once they enter the usual care environment.

Leverage Investigator and Patient Networks

Study start-up activities, including site recruitment, contracting, regulatory document collection, and training, are key drivers of total study cost regardless of the type of study executed. Therefore, strategies such as the early identification and implementation of a network of investigators who agree to a mandate to support a program of synergistic studies over time will result in measurable cost and timeline efficiencies. Once enrolled in a research network, pre-screened investigators amenable to participation in multiple studies and sub-studies will contribute to decreased start-up time and burden from one study to the next. While randomized controlled trials (RCTs) typically require the involvement of academic or specialty care centers, observational studies generally draw upon the same mix of study sites that better reflect routine medical care. It is postulated that this approach would ensure broad unselected populations, avoid competition between RCTs and registries, and stimulate and encourage scientific and clinical input from academia.

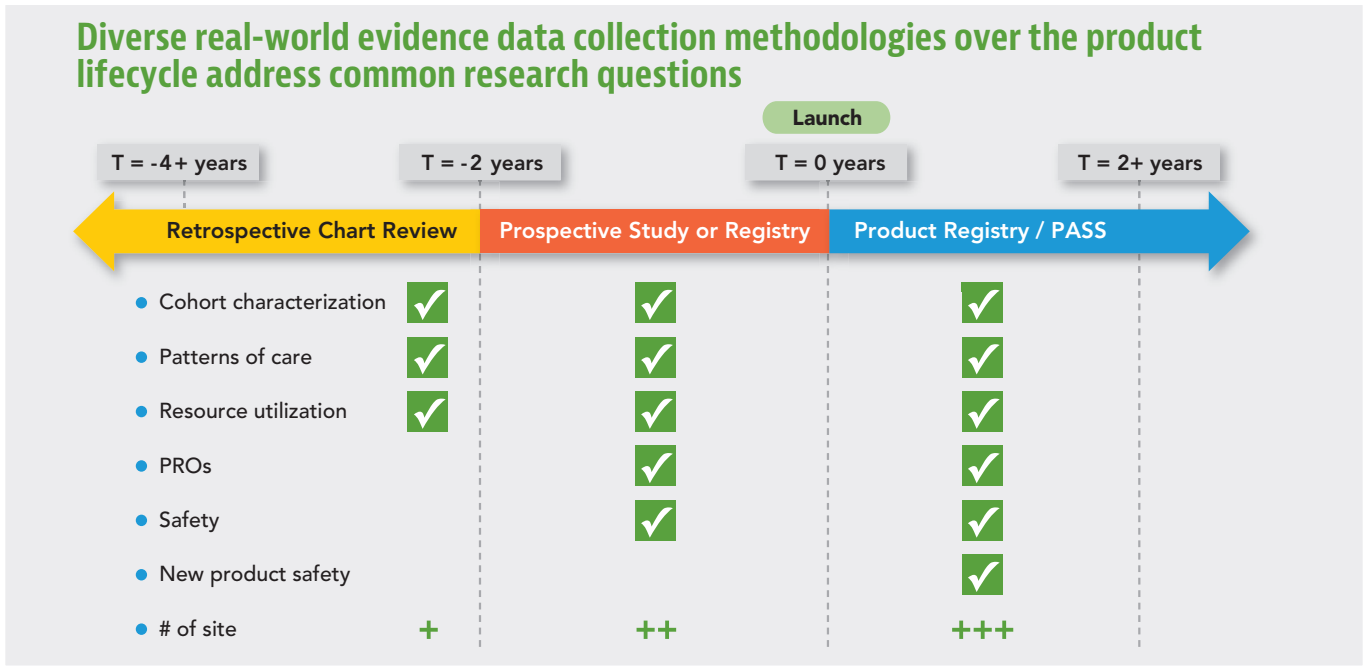
Reliance upon pre-existing networks of patients is also an appealing strategy for recruitment and enrollment. Electronic medical record (EMR) or other health data, including diagnostic and pharmacotherapy information, can be analyzed to identify potentially eligible patients, or alternatively, populations of patients can be built expressly for the purpose of study participation. Additionally, numerous online, high volume, international panels of pre-consented and screened populations of patients have been established that can support scientifically rigorous international burden of illness assessments.[5] Popular patient support and advocacy organizations can also be utilized to access specific patient cohorts of interest.[6]

Prioritize Innovation and Technology

Traditional approaches to real-world data analytics are constrained by available programming resources and, typically, require custom programming for each analysis. Moreover, format and programming differences across study datasets make it inefficient to execute and difficult to meaningfully compare outcomes.[7] These challenges may be resolved through standardization – in particular, through the use of a common data model (CDM), such as that developed by the Observational Medical Outcomes Partnership (OMOP)[8] and currently maintained and used for research by the Observational Health Data Sciences and Informatics (OHDSI) collaborative.[9]

Using a CDM to develop study CRFs and standardized data formats allow for the pooling of data from de novo data collection studies as well as data from secondary

Figure 3. Stepwise approach to the integration of multiple real-world studies



administrative claims or EMR sources resulting in tailored repositories of patient-level data. A CDM approach to evidence generation also allows for the use of technology-enabled automated data analytics platforms, such as Evalytica[10], which permit "faster time to data." Data insights sooner can support strategic and timely data dissemination and reporting, as well as to inform the design of subsequent downstream studies – or even result in the adaptation of a current study design through an amendment prior to close-out.

Designing and implementing an optimal electronic data capture and communications infrastructure early in the product commercialization process can also result in significant efficiencies. Innovative, multimodal EDC systems far exceed basic data capture capabilities in terms of core functionality. A tailored, fit for purpose EDC system can serve as an epicenter of research activity, facilitating study recruitment and enrollment, data capture and management, and global study communications. Study Coordinating Centers can use such systems to manage multiple studies across multiple study sites simultaneously, as well as to enhance study and data quality in real time. Investigators can access these infrastructures to enter study data, download study reports and their own data reflecting their patients' clinical and study outcomes, and learn about new studies opening for enrollment.

Synergies and efficiencies across a program of studies resulting from early investment in an EDC infrastructure can be realized, particularly in relation to common core data elements. There will be significant overlap in key variables such as patterns of care, resource utilization, and clinical outcomes of interest. By creating libraries of e-CRF common data model formats, data dictionaries, statistical analysis plans and associated programming code and validation rules, and drawing upon these investments from one study to the next, research time and costs can be greatly reduced. This approach will also result in consistency across study datasets which will permit the pooling and cross-analysis of standardized data from multiple studies, especially important in the context of increasing comparative effectiveness evidence requirements.

Increase Your Return on Evidence Gathering Investments

Late phase strategic and synergistic real-world evidence gathering across the product lifecycle can and will contribute significantly to cost and timeline efficiencies. To this end, the following general recommendations may be useful.

- Engage in early and rigorous value development planning including the delineation of a tailored real-world data strategy. A plan which clearly delineates the "right" real-world data for the "right" audience at the "right" time will ensure that data collection efforts are focused and coordinated and contribute to successful reimbursement and market access outcomes.
- Design studies in stepwise and strategic fashion, and strive to combine designs and research objectives into

a reduced number of study protocols where possible. The integration of multinational chart review studies and disease and product registries are particularly well-suited to this synergistic approach.

- Build CRFs and underlying data structures using a common data model to permit advanced and automated data analytics across various pooled data sources.
- Establish a central repository of study documents and materials including protocols, e-CRFs, statistical analysis plans, CDM data formats, and coding to ensure optimal use and re-use of fixed cost investments.
- Implement an EDC infrastructure early in the product lifecycle to support a standardized approach to the collection of key data elements, investigator communications, and recruitment within and across studies.
- Build a network of investigators who are committed to a well-described, scientifically rigorous, multi-year program of complementary studies.
- Initiate network study sites with a mandatory core study protocol designed to achieve a standardized, longitudinal core minimum dataset. Offer subsequent opportunities for new and existing sites to "opt in" to additional studies and sub-studies of interest through notifications communicated via the EDC infrastructure.
- Offer participating investigators opportunities to access their own data electronically in real time. Benchmarking patient data within and across study sites through the use of customized reports and data visualization techniques can serve as an effective participation incentive by offering investigators important clinical information as well as opportunities to participate directly in study publications.

An early adoption and implementation of strategic study designs, operational infrastructures, and technology-enabled data analytics can provide important opportunities for significant savings in terms of commercialization timelines, costs, and human resource requirements. Though this approach does demand a greater investment earlier in the product lifecycle in relation to the planning and execution of real-world studies, the return is likely to exceed expectations. As research dollars decrease and evidence requirements increase, new and sustainable research strategies and methodologies that contribute to a high quality, on-time delivery of an evidence base that meets market access stakeholder requirements are clearly warranted.

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Data Needs and Challenges in Cancer Epidemiology: A U.S. Real-World Database Perspective

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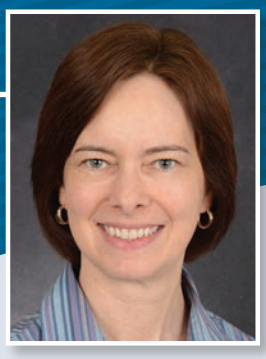


Beth Nordstrom

Introduction

With treatment options for many types of cancer increasing, there is an escalating demand for real-world evidence in oncology. The safety and efficacy of new antineoplastic drugs are demonstrated in clinical trials before U.S. Food and Drug Administration (FDA) approval, but are these treatments safe and effective for the patients prescribed these drugs in medical practice outside of trials? How are these drugs being prescribed by oncologists? Which patients receive which drugs? How long do they stay on treatment? Questions such as these can be answered only through real-world observational data.[1]

Evidence-based cancer epidemiology research using observational real-world data poses special challenges seldom found in other therapeutic areas. Treatment for cancer is often very complex, with multiple drugs given in combination regimens that frequently change over time. The course of cancer treatment may span many years, much longer than the average time an individual patient is tracked in many data sources. Progression-free survival is a high-priority target outcome, but can be exceedingly difficult to ascertain without the close, regular monitoring that occurs in clinical trials. Adverse events can be difficult or impossible to attribute to any particular treatment, given the treatment combinations used (both antineoplastic and as supportive care), and many adverse effects may be brought about by the disease itself and unrelated to treatment. Some studies examine cancer as an adverse outcome to treatment for non-cancer-related conditions; for these, the association between drug use and cancer may be difficult to assess due to long latency periods and the potential for unmanageable degrees of bias and confounding.[2]

"Evidence-based cancer epidemiology research using observational real-world data poses special challenges seldom found in other therapeutic areas."

In the United States, there are two primary types of real-world databases available for oncology research: electronic medical record (EMR) data and administrative claims data containing medical and pharmacy claims information. The advantages of using these types of electronic databases for research are typically large patient population sizes, relatively timely updates to and availability of the data, and inclusion of many required data elements, such as patient diagnoses, medical procedures performed, inpatient admissions, and drug prescribing or dispensing. EMR databases often contain additional data elements relevant to oncology research, such as laboratory test results and detailed clinical information. In some cases, data from an EMR or claims

database can even be supplemented with linked data from other sources, such as chart reviews, primary data collection such as patient or provider surveys, or registry data.

Cancer Epidemiology Database Study Types

Numerous oncology topics can be investigated using real-world databases. Incidence and prevalence studies look at rates of cancer relative to the general population, or to subgroups of the population with a particular disease or set of clinical or demographic characteristics. Patients with cancer can be followed for health outcomes such as disease progression, remission, or complications in studies that focus on the natural history of disease rather than on the effects of treatment. Treatment pattern studies examine the various antineoplastic or supportive care agents used to treat cancer patients in real-world settings and can identify the characteristics of patients prescribed each drug or regimen, their use across lines of therapy, and drug utilization measures such as adherence and persistence.

Drug safety and effectiveness are often investigated using real-world databases. Although treatment effectiveness can be very difficult to measure using real-world data, outcomes such as overall survival and, for hematologic cancers, key lab values indicating the likely effect of treatment can be studied. Many antineoplastic drugs carry a high burden of adverse events, and even supportive care oncology drugs have been associated with adverse outcomes. The incidence rates of these adverse events can be examined in databases. Finally, safety studies may be conducted to look for new-onset cancer as a safety outcome from the use of drugs intended as treatment for other diseases.

Real-World Databases for Oncology: What Is Available?

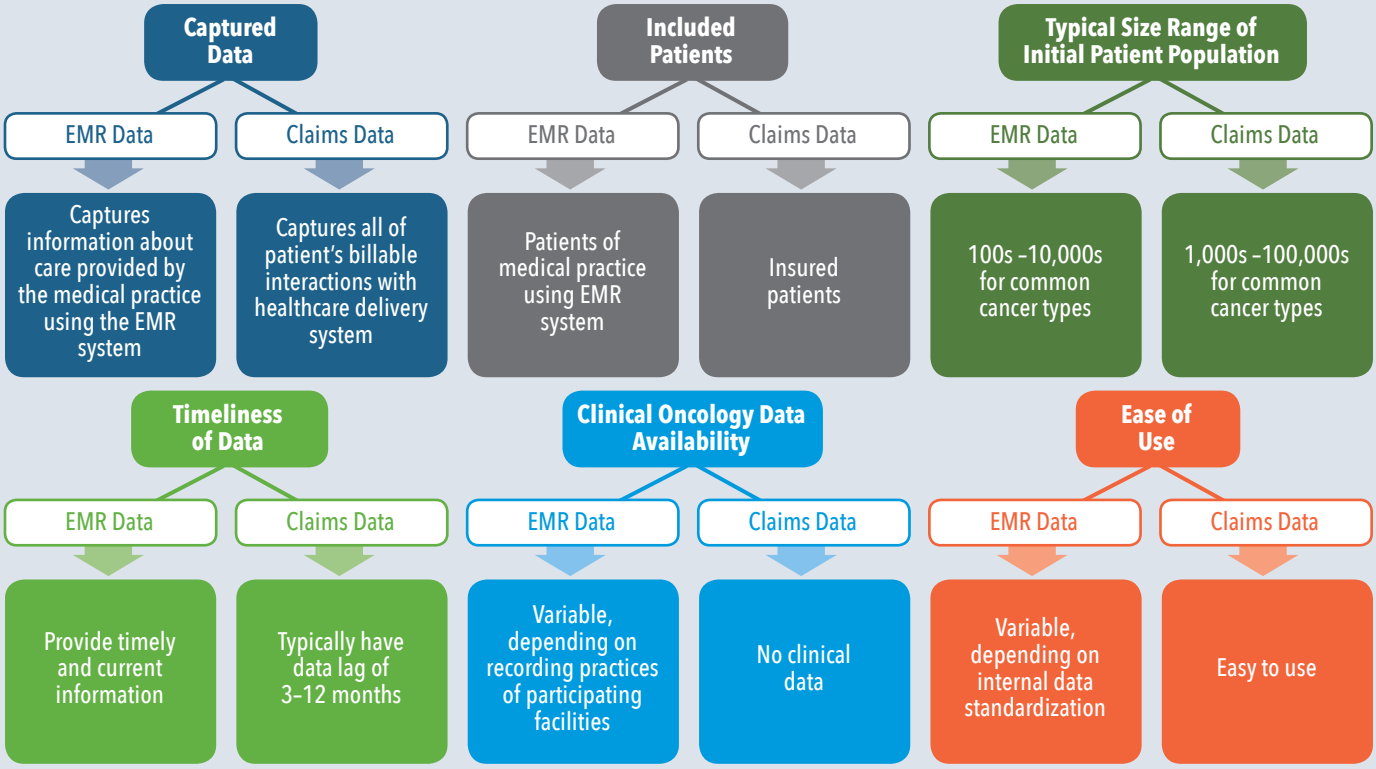
Insurance claims data summarize all of the billable interactions of an insured patient with the healthcare delivery system. These data include the dates corresponding to a variety of billing codes submitted to payers, including codes representing disease diagnoses (ICD-9, ICD-10), medical procedures (HCPCS, CPT4), and pharmacy drugs (NDC). In a closed system that contains data from payers, the claims data provide a complete picture of all covered medical and pharmacy services received by a patient in a clear, standardized format for a large number of insured patients. Open claims systems, which contain data from providers rather than payers, can be even larger than closed systems but are not complete for all patients, as not all providers caring for a given patient may submit claims to the same system.

EMR databases have many of the elements of claims data but also contain additional clinical information that is highly relevant to oncology studies. Some EMRs are designed to be used specifically in outpatient oncology clinics that provide treatment to cancer patients, making them a valuable real-world evidence data resource specifically for oncology studies. Other EMR databases not specific to oncology clinics may also be used for cancer epidemiology studies if the particular practice using the EMR system provides care for cancer patients. Some of these more general EMR databases have developed their own cancer "registries" containing in-depth information on histology, staging, treatment, and progression derived from progress notes and other data not typically included in an EMR extract.

Figure 1. Types of evidence-based cancer epidemiology studies

Incidence/Prevalence	Treatment Patterns	Drug Safety of Antineoplastic Agents/Supportive Care
Derive incidence or prevalence of type(s) of cancer relative to population or relative to patient populations with different demographic characteristics	Identify drugs and combinations of drugs being used to treat different types of cancer, during different lines of treatment	Examine adverse events associated with the use of antineoplastic drugs or supportive care agents prescribed to cancer patients
Natural History of Disease	**Treatment Effectiveness**	**Drug Safety with Cancer as Adverse Event**
Estimate the incidence of disease outcomes and complications among cancer patients, irrespective of treatment	Find the incidence of beneficial health outcomes associated with antineoplastic or supportive care treatment	Estimate the incidence of cancer as an adverse event associated with the use of drugs not given to treat cancer

Figure 2. Comparison of data sources used for oncology studies



Data Needs for Oncology Studies: How Can We Fill the Gaps?

While insurance claims databases provide a comprehensive picture of a patient's medical care, they lack the clinical detail needed for many oncology studies. For example, claims data can indicate whether a medical test was conducted, but in general, the results of the test are not available. Some claims databases have linked laboratory results available, but usually for only a subset of patients and tests, so that the available data may be highly non-representative of lab results for the full patient population in a study. Diagnosis codes found in claims data are not confirmed and may indicate a diagnosis that was suspected but then ruled out by a given diagnostic test. Claims databases also lack clinical details such as cancer staging at initial diagnosis or progression over time. Metastatic cancer can in some cases be identified through diagnosis codes indicating a secondary tumor and/or treatment specific to metastatic cancer, but this approach is imperfect at best, and distinguishing among earlier stages in claims data may be even more difficult.[3]

EMR databases can help fill some of these gaps, as discussed above, but they have their own limitations. EMR systems are designed to help medical providers manage patient care and the business aspects of their practices, such as billing and scheduling. Diagnoses entered into an EMR may be no more valid than in a claims database, with rule-out codes and other erroneous diagnoses that do not reflect the patient's true medical conditions. While an EMR database may provide the opportunity to include data elements important for research – such as disease progression, comprehensive medical histories, and additional treatments administered outside of the practice – the availability and completeness of these data elements varies both across and within EMRs, depending on how each practice choses to enter data and to use the EMR for their own purposes. Information is often entered into an EMR as unstandardized free text, which then needs extensive cleaning and standardizing prior to initiating data analyses.

Despite these limitations, some cancer epidemiology studies can be conducted within a claims or EMR database and still produce valid results, as long as the needs of the study make use of the data source's strengths and do not rely on data elements that are absent or incomplete. For example, studies examining outpatient cancer treatment patterns or incidence of adverse events measured through validated coding algorithms or outpatient lab tests can be completed in an appropriate database. Yet many important research questions in cancer epidemiology cannot be answered through claims or EMR data alone. Many drug safety studies, for example, require detail from both inpatient and outpatient settings, where the adverse events under investigation are not reliably identified through ICD-9 or ICD-10 codes. Additional data gaps may include insufficient depth of clinical detail around the cancer at

the start of follow-up, or around changes over time such as tumor size or response to treatment.

Approaches to filling these gaps may include linking to external data sources that contain the missing information or collecting data either retrospectively or prospectively. One commonly used linked database for oncology research is the SEER-Medicare database[4], which contains Medicare claims data combined with the cancer registry information collected by SEER (the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute). The SEER data provide important clinical information from the time of initial cancer diagnosis that is missing from the claims data, including records of cancer type and stage, while the Medicare data for the subset of patients with drug coverage should be complete for services covered by Medicare, including cancer treatments and outcomes. This database is limited, however, by having a several-year lag time for the SEER data, as well as lacking follow-up registry or EMR-level data (e.g., lab results or disease progression).

Retrospective data collection typically involves chart review, which can be performed through text searches in electronic data if the information sought is recorded electronically (e.g., progress notes, radiology reports), or via manual review of paper charts. Even in pure EMR databases, where all records are kept electronically, data extracts generally cannot include free-text information because of concerns for patient privacy, and hence require an electronic chart review. Chart reviews can be used to validate diagnoses that qualify patients for the analysis or that occur as outcomes during follow-up, or to pull information that is missing in the data extract, such as results of a lab test that were not entered into the database. The chart review targets only the specific information that is needed, which can make it much more focused and study-appropriate than a database extract, but it can be time-consuming and expensive. Additionally, in many cases the required records for some patients are not available for review, leading to problems with missing data that need to be addressed.

Some topics in cancer epidemiology, such as assessing treatment response when the data needed to evaluate it are not usually measured in real-world clinical practice, require prospective data collection. Patients qualifying for the analysis are identified through a claims or EMR database, and the patients and/or their physicians are contacted to request enrollment in a prospective study. These endeavors may involve patient surveys to examine self-reported information from qualifying patients such as patient-reported outcomes, physician or caregiver surveys that inquire about their perspective on the patient's treatment or condition, blood draws or collection of tissue samples from patients to measure outcomes or biomarkers not assessed in the course of their medical care, or even enrollment into a registry with scheduled visits and examination of many follow-up characteristics and outcomes. Although these studies are by far the most expensive and time-consuming of the observational study types, they have an unsurpassed advantage in allowing investigation of exactly the information needed for the study.

Conclusion

Although many sources of real-world evidence are available to conduct cancer epidemiology studies, the data needs of these studies are not always fully met by a single data source. EMR databases lack complete information about diagnoses and treatments from outside the EMR practice, and the data entry can be highly idiosyncratic. Clinical details such as cancer staging and progression may be present for some patients but missing for many. While insurance claims data cover large patient populations, give complete data on all of a patient's billable medical care, and are easy to use, they are usually inadequate for many oncology studies due to their lack of clinical data. Data collection can help to overcome many of the shortcomings of these databases, but require markedly greater time and expense, as well as permission to collect the additional data. Ideally, more comprehensive oncology datasets could be constructed by linking together existing databases.

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Real-World Evidence and Social Media: Case Studies

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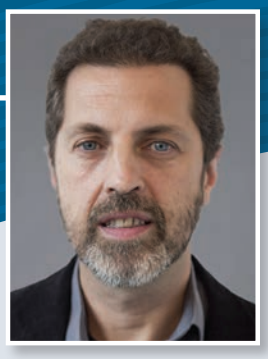


Andrew Cox

The analysis of social media is becoming a powerful tool that is being used increasingly to answer research questions across numerous areas including disease spatiotemporal epidemiology and drug adverse events. Patients are increasingly using web technologies such as social media (e.g., Twitter and Facebook), blogs, and forums to generate and access opinions of diseases and treatments. For rare diseases, patient social media is important to the patient population as it represents one of the few means of contacting others with the condition. There are specific forums for almost every disease and condition. Many contain large volumes of patient posts, posted by a community of hundreds, thousands, or tens of thousands of patients with the discussion records often reaching back several years. Treatments, treatment options, and symptoms are often the largest topic of conversation, with a growing trend for posters to summarize their entire treatment and test history, with dates, in the footer of their postings. Other metadata included in the posts often contains information on join date, posting date and time, and sometimes geolocation. In addition to monitoring adverse drug events, social media can provide a means of mapping the symptoms, treatments, outcomes, and development of rare and less well characterized conditions where published accounts are lacking. This vast volume of content therefore serves as an important potential source of real-world data that can be used for pharmacoepidemiology and other research.

However, there are barriers to effective use of this real-world data, as dealing with text in social media settings is hugely challenging. Different styles of communication, shorthand, typos, spelling mistakes, and contextual meaning all make analytical approaches difficult. For example, within a collection of posts on breast cancer the treatment Docetaxel can be referred to as 'tax', 'doci', 'docy', 'docitaxal', 'dositaxal', 'dositaxel.' Words also often need to be accounted for in context. Using the same example where the 'tax' abbreviation is used, it is necessary to differentiate the statements "yesterday my specialist put me on tax" and "hoping to receive a tax rebate." We present two case studies which attempt to give a flavor of the potential of patient-related social media as a data source.

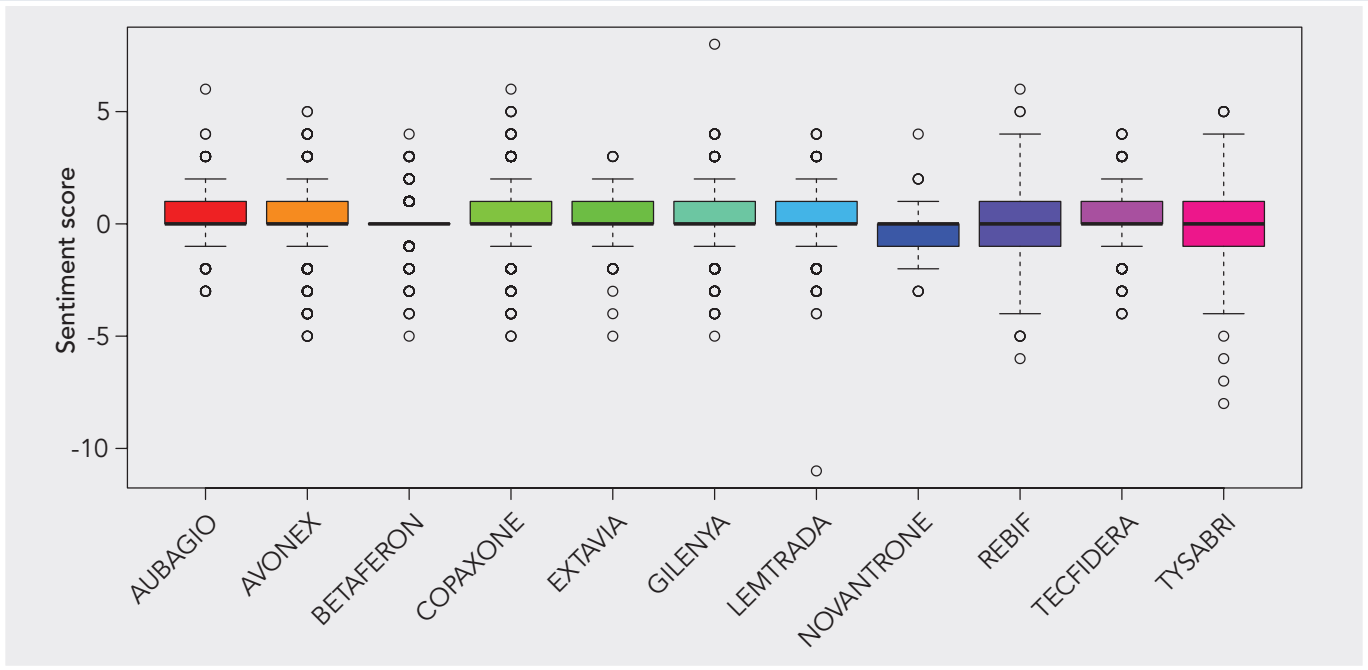
Case Study 1: An Analysis of Tweets about MS

Multiple sclerosis (MS) is a chronic, neurodegenerative autoimmune disorder of the central nervous system and is the most commonly acquired neurological disorder in young adults. Given the age of the patient population and recent availability of many therapies for MS, we explored whether we could analyze social media to help gauge patient opinion about MS treatments.[1]

We used the popular social media site Twitter (http://twitter.com) to explore the reporting of patient opinion about MS treatments. We found approximately 60,000 tweets relating to an MS treatment.

In order to analyze text, *Natural Language Processing* had to be employed. Natural language processing (NLP) is a way for computers to analyze, understand, and derive meaning from human language in a useful way. Because of the short nature of tweets and the presence

Figure 1. Boxplot of sentiment scores of tweets



of typographical errors, ad-hoc abbreviations, phonetic substitutions, ungrammatical structures, and emoticons, NLP was first used to essentially "clean the data" and make better sense of the tweet texts.

NLP was then used to perform sentiment analysis. Sentiment analysis is the process of computationally identifying and categorizing opinions expressed in a piece of text, especially in order to determine whether the writer's attitude towards a particular topic or product is positive, negative, or neutral. A sentiment score can then be generated - positive scores indicating a preferential statement or negative scores a disapproving one.

In our analysis, we found that about half of all tweets had a neutral sentiment. Combining tweets that contained sentiment showed a significantly different mean sentiment score between drugs (see Figure 1).

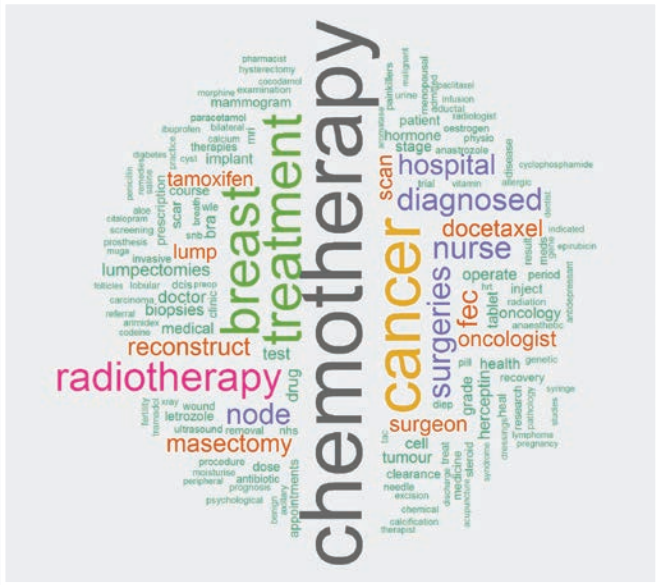
Most common words in tweets for treatments were also investigated and word clouds generated. A word cloud is an image composed of words used in a particular text, in which the size of each word indicates its frequency. An example word cloud for the 50 most common words for one treatment investigated here is shown in Figure 2, highlighting potential adverse events "pml" and disease activity "relapse."

Overall we concluded that a significant proportion of tweets did contain either positive or negative statements about MS treatments, and the distribution of sentiment score was different between treatments. Thus it appears that Twitter can be a potential resource to understand patient opinion about MS treatments. When looking at frequency of words, words known to be associated with particular drugs (e.g., "infusion") were identified providing some face validity for our results reflecting real, specific tweets about MS treatments.

Figure 2. Word cloud for one MS treatment

Figure 3. Word cloud for words tagged "symptom/side effect" related from breast cancer postings

Figure 5. Word cloud for words tagged "medical" related from breast cancer postings



Case Study 2: Characterising Breast Cancer

In this simple analysis, over 120,000 posts spanning several years were collected from leading breast cancer discussion forums. Posts were processed to "tag" emotional words, medical words, and words related to symptoms/side effects. Term heterogeneity (variation in words with the same intended meaning) was accounted for by the creation of word variant dictionaries. Once words were corrected from variants, word frequency tables were produced for each tagged category of word type. Word clouds were produced from the word frequency tables.

Figure 4. Word cloud for words tagged "emotional" related from breast cancer postings

These results represent what can be potentially done relatively quickly and easily using data from Twitter. More rigorous analytical methods can be applied for more specific questions (e.g., the analysis of adverse events, treatment preferences and switches, and investigations of disease epidemiology).

The evolution of healthcare, the high cost of certain drugs, the competition of new drugs entering the market, and the need to show how treatments really work in the real world have all had a part in increasing the importance and value of real-world evidence (RWE). As the demand for RWE grows, the definition and scope of what that evidence entails also grows, and patient input via social media is becoming a very real part of building the RWE story. While the case studies in this article show a fairly simplistic use of social media in this way, the options of its use in representing true value from the patients' perspective are limitless and will continue to evolve. Social media is here to stay, and in many cases is the primary way for patients sharing a common disease, health state, or treatment to share real-world experiences. As such, social media has become a source of real-world evidence that cannot be ignored.

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What is Influencing Pricing and Reimbursement in 2016?
Policy Trends Identified by Payers

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Market access is the ultimate goal for healthcare treatments, however, priorities and decision processes can vary from country to country and can change quite often. To gain insight into what factors affect a product's access in various markets, Evidera has established a Pricing and Reimbursement Policy Council (PRPC) composed of current and former payers from six countries, including Germany, Italy, Spain, England, France, and the U.S. This council meets on a quarterly basis, in addition to debates and discussions via blog throughout the rest of the year, to identify changes in policy trends across the markets that may affect and influence changes in pricing and reimbursement (P&R).

Below is an overview of the trends identified by the PRPC that they feel will have the greatest impact in 2016.

ONCOLOGY	Immuno-Oncology (primary area of concern)	Combination Treatments (secondary area of concern)

Segments of Payer Concerns	Trend Examples (Non-exclusive and may apply to other conditions)
P&R Process Changes / Adjustments	• CDF (Cancer Drugs Fund)[1] and Highly Specialized Technology (HST) evaluations[2] • Opening the debate on process changes in orphan drug assessment • Accelerated access review and adaptive pathways • Reducing time of pricing negotiations
Cost Concerns	• New contracting arrangements • Price per indication/ patients • Increased portfolio contracting • New contracting arrangements "package deals" • Specific focus on claw-back clauses and utilization of performance contracts and real-world evidence (RWE) to reassess prices
Methodological Concerns	• Long-term efficacy benefits and uncertainty of data in early access • Quality of Life (QoL) data: missing values • Adverse Events (AE) data: survival analyses, "progression related" events, AE selection itself (e.g., special events for assessment) • Added benefit based on lesser harm – request for non-inferiority in benefit

Selected countries of PRPC (5 EU and U.S.) *Almost all countries of PRPC (5 EU and U.S.)*

ORPHAN	New molecules / new indications (primary area of concern)	Number of available molecules in one indication (secondary area of concern)

Segments of Payer Concerns	Trend Examples (Non-exclusive and may apply to other conditions)
P&R Process Changes / Adjustments	• Highly Specialized Technology (HST) evaluations[2] • Opening the debate on process changes in orphan drug assessment • Accelerated access review and adaptive pathways • Different reimbursement routes for indication extensions
Cost Concerns	• Increased contracting and risk sharing • Pre-defined budget by indication – multiple drugs share available budget
Methodological Concerns	• Uncertainty of data in early access and expression of patient benefit • Endpoints and statistically relevant demonstration • QoL data: missing values

Selected countries of PRPC (5 EU and U.S.) *Almost all countries of PRPC (5 EU and U.S.)*

CHRONIC INDICATIONS	New disease states (e.g., nonalcoholic steatohepatitis – NASH) (primary area of concern)	New molecules in low cost environment (e.g., PCSK9 for cholesterol) (secondary area of concern)

Segments of Payer Concerns	Trend Examples (Non-exclusive and may apply to other conditions)
P&R Process Changes / Adjustments	• Assessment of older drugs already on the market (recurring trend) • Exploration of limiting prescriptions in markets where specialist prescribing is currently not an option
Cost Concerns	• Chronic diseases and their "business case" – hurdle of generic standard therapies as price reference (e.g., diabetes, hypertension) • Increased contracting and risk sharing • Agreed final price retroactively valid from market entry (or defined period of time) • Making information on final prices available
Methodological Concerns	• Missing long-term data at market entry • Measuring progression-related events

Selected countries of PRPC (5 EU and U.S.) *Almost all countries of PRPC (5 EU and U.S.)*

BIOSIMILARS	Economic case for biosimilars and change of prices for branded products	What may be the budget impact if switching is an option?

Trend Examples (Non-exclusive and may apply to other conditions)
Extension / introduction of Rx quotes
Management of formulation changes of branded products
Continuous evaluation against branded reference products

■ *Selected countries of PRPC (5 EU and U.S.)* ■ *Almost all countries of PRPC (5 EU and U.S.)*

Most Dominating* Trends across All Markets and Indications

1 Contracting and new ways to price drugs

2 Changes in assessment and pricing of orphan drugs (process and methods)

3 Methodological adjustments including route or access (early/regular) and indication (including patient benefit demonstration, long-term morbidity/mortality, data uncertainty, progression related AEs, role of RWE, etc.)

** Most frequently mentioned by the PRPC between January – March 2016, across all six participating countries (Germany, Italy, Spain, England, France, and U.S.)*

If you have questions or would like to share the trends you have identified (confidentially), please contact marketaccess@evidera.com. Questions and comments are encouraged and welcome, and updates will continue to be made available.

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Incorporating Patient Preferences into Product Development and Value Communication: Why, When and How?

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Introduction

Should you be incorporating patient preferences into the assessment of the benefits and risks of your drugs and devices, and if so, when and how? As the importance of patient preferences is acknowledged by regulators and payers, we are often asked these questions by our clients. Responding to the demand for this type of work, Evidera has formed a dedicated Patient Preference team to help our clients implement and use appropriate patient preference elicitation techniques and associated decision analysis tools.

The focus of this new Patient Preference team differs from our established expertise in Patient-Reported Outcomes (PROs). While PROs are designed to measure a patient's perception of a health state, patient preference data is designed to assess the way patients make trade-offs between treatment attributes. Regulators' interest in PROs will continue, but they are also showing more and more interest in patient preference data.

This article summarizes recent developments in the use of patient preferences in decision making, the implications for evidence generation planning, and recent guidance on which patient preference methods are the most appropriate.

Patient preferences are increasingly required by decision makers

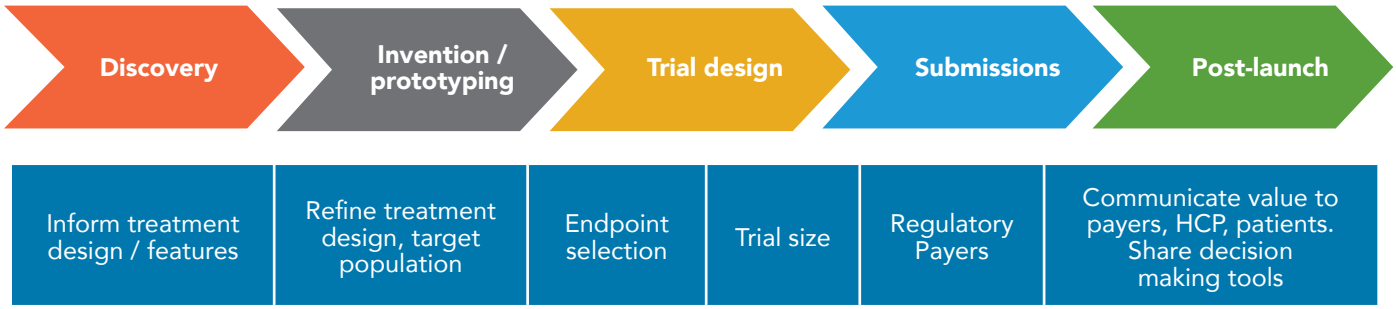
Most people would recognize that patient preferences have an important role to play in healthcare decision making, although it is only recently that decision makers have shown interest in quantitative methods for eliciting patient preferences. Previously, the patient's role in health policy development was mostly limited to representation on decision making committees.[1-3] Increasing recognition of the limitations of such an approach – focusing on the qualitative input of a small number of not necessarily representative patients, as only one voice in a large decision making group – has led to calls for the rigorous quantification of the patient voice.[4]

Regulators in the United States are responding to this call. This is illustrated by the United States Food and Drug Agency's (FDA) recent encouragement to device manufacturers to submit patient preference data as part of submissions, and their consultation on how best to collect this data.[5] This has coincided with the first regulatory approval by the FDA based on preference data.[6] In this instance, the Center for Devices and Radiological Health (CDRH) used patient preference data to determine whether the benefits of a weight-loss device (percent weight loss, weight loss duration) outweighed its risks (mortality). Partly on the basis of this analysis, they concluded that the device should be approved.

Similar developments are taking place in Europe with regulators and health technology assessment (HTA) agencies making use of patient preferences. Staff at the European Medicines Agency (EMA) recently published a manuscript outlining the piloting of methods to incorporate patient preferences into the assessment of oncology treatments.[7] They concluded that "our preference elicitation instrument was easy to implement and sufficiently precise to learn about the distribution of the participants' individual preferences." In Germany, the Institute for Quality and Efficiency in Healthcare (IQWiG) has successfully piloted techniques for eliciting and incorporating patient preferences into its economic evaluation methods and incorporated these methods into its methods guidance.[8]

These examples represent just the formal requirements of decision makers. But even where it is not yet formally required, patient preference data is being collected and submitted to decision makers. This research is being commissioned by several stakeholders, not the least of

Figure 1. Multiple uses of patient preference data in product development



which are patient advocacy groups.[9] Further, it is hard not to see these developments as part of a broader trend to more systematically incorporate patient preference data into decision making. We watch with interest as, for instance, the FDA and industry negotiate the next round of the Prescription Drug User Free Act (PDUFA VI), which is expected to establish standards for conducting and analyzing patient preference research, and take steps to formally integrate patient preferences into regulatory decisions.[10,11]

Implications for evidence generation planning

The interest of decision makers in patient preferences has a number of important implications for how manufacturers should generate and use such data. Many of our health economics and outcomes research clients are familiar with collecting patient preference data using some form of a conjoint analysis as part of their marketing strategies. Given the expanded role of patient preference data, manufacturers will need to start planning for the collection of this data much earlier, with applications throughout the product lifecycle (see Figure 1).

For instance, combining patient preference data with data on the performance of treatments using decision modeling techniques, regulators are estimating the overall benefit-risk of a product. A similar analysis can be used to estimate patients' maximum acceptable risk (MAR) – the maximum likelihood of a certain risk a patient could tolerate in exchange for the benefits generated by a treatment. This data can be used to inform trial size calculations, ensuring a trial is powered sufficiently to demonstrate that the risk of a product is lower than the MAR.

Given the importance of these considerations to the chances that a treatment achieves authorization and reimbursement, it is natural to cascade these requirements back into the discovery and invention / prototyping stages of the product development cycle to ensure that treatments are designed in line with patient preferences to secure a positive regulatory response. As a consequence, it is important to plan patient preference studies as early in the development process as possible.

For which products should patient preference data be collected? It is currently difficult to offer a definitive answer to this question, though it is possible to point to trends that will help determine the value of patient preference data on a case-by-case basis. First, is the product a device? The CDRH encourages manufacturers of medical devices to include patient preference data in their submissions, and, as we noted above, there is a precedence of such preference data informing the CDRH's decision. Second, is a decision likely to be preference-sensitive? Regardless of whether a product is a device or a drug, a benefit-risk assessment is more likely to be preference-sensitive if:

1. A product generates clear clinical benefits but has a greater risk of events that are likely to concern regulators, such as potentially fatal side effects.
2. A product generates similar benefits to standard of care, but with a different safety profile.
3. A product is in a crowded market, with no obvious preferred treatment.

Designing a credible and useable patient preference study

Designing and implementing patient preference studies, as well as the interpretation and application of the data, poses a number of challenges, including: the selection of a credible preference elicitation instrument; ensuring data is collected from a representative sample of patients; and generating outputs that are useful for decision makers. In this section we focus on just one of these, selecting a credible preference elicitation instrument. Recent reviews have identified many relevant methods (see Figure 2).

For those unfamiliar with the field of preference elicitation, the number of methods available can be overwhelming. Particularly given the lack of guidance as to the most appropriate method for a particular circumstance, and the use of different methods by

Figure 2. Methods for eliciting patient preferences[12]

Category		Method
Indirect	Choice based	Discrete choice experiment
		Best-worst scaling
	Matching	Time-trade-off
		Standard gamble
Direct	Ranking	Simple Multi-Attribute Rating Technique Exploiting Ranks (SMARTER)
	Rating	Visual analogue scales (VAS)
		Point allocation e.g., SMART
	Threshold analysis	
	Pairwise	Analytical Hierarchy Process (AHP)
		Measuring Attractiveness through a Categorical Based Evaluation (MACBETH)
	Swing weighting	Simple Multi-Attribute Rating Technique with Swings (SMARTS)
	Scoring rules	Bi-section method
		Difference method

different decision makers - with the FDA's first approval informed by preference data being based on the findings of a discrete choice experiment, the EMA piloted a variant of swing weighting, and the IQWiG explored both the analytical hierarchy process and discrete choice experiment.

The appropriate method is a function of:

1. The objective of the analysis, including whether it is intended to support internal decision making or regulatory submission;
2. The patient population, including whether they experience any cognitive impairments; disease prevalence; and likely diversity of preferences;
3. Lessons from previous experience of applying the method for a particular purpose;
4. Good practice guidelines.

Focusing briefly on the latter point, comprehensive good practice guidelines are not yet available, but guidance is starting to emerge. For instance, the Medical Devices Innovation Consortium (MDIC) recently published a description of some of these methods[12], and the recent outputs from the International Society for Pharmacoeconomics and Outcomes Research's (ISPOR) Multi-criteria Decision Analysis Taskforce identified the differences between many of these methods and outlined both theoretical and practical principles that might be brought to bear on the choice of methods.[13,14]

More precise guidance is expected as the demand for patient preference data increases. A key source of such guidance could be the Innovative Medicine Initiative's call for research on eliciting the patients' perspective on the benefits and risk of medicinal products.[15] This project will not be completed for a number of years, but in the meantime, Evidera's Patient Preference team will be sharing expertise on this topic in upcoming webinars and publications.

Conclusion

A significant effort is committed to the quantification of clinical and safety endpoints to inform healthcare decision making. This is completely appropriate if we are to make decisions that benefit patients and society

more generally. Another important consideration, however, is that until recently, patients' preferences for these attributes have not received the same amount of attention. We are pleased to acknowledge changes in this attitude, and the increased quantification of patient preferences to inform decision making. While we have just started to determine precisely how patient preferences should be collected and incorporated into decision making, these are exciting developments, and we look forward to participating in a scientific discussion that will further advance these techniques.

In the meantime, given decision makers' interest in patient preference data, manufacturers should be systematically considering the collection of such data in their evidence generation planning and getting expert input into the design and implementation of these studies.

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Rolling the DICE: Discretely Integrated Condition Event Simulation for Health Economic Analyses

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As part of a health technology assessment (HTA), there is commonly an analysis of the economic and health implications of paying for a new technology. This analysis is nearly always based on a mathematical framework that provides for integrating information from the relevant clinical trials with data from other sources to forecast what will happen if the new technology is used in place of an existing one. These models are developed using some organizing constructs.

The technique most commonly used today organizes the model around the states that people can be in and transitions among them (i.e., a Markov model).[1] While Markov states can be applied to many aspects of a disease and its management, they are restricted by several strong requirements: any given group of people can be in only one state at a given time and that group must be homogeneous in terms of the transition probabilities. These make it difficult to properly capture our increasingly sophisticated knowledge about the factors that determine the course of illness and the characteristics (e.g., biomarkers) that imply a better response to an intervention in a given person. Moreover, HTA agencies and their expert advisers have become increasingly sophisticated and demanding.

One alternative to Markov models is discrete event simulation.[2] While this technique was developed for operations research and focuses on competition for resources and resulting queues, it has been adapted for use in HTA.[3] The technique organizes the model around events instead of states and offers multiple constructs, like entities, attributes, resources, queues, and an explicit clock. Many of these can be leveraged for economic analyses, but for most applications, they are unnecessary, and specialized software is required for implementation.

Modelers in our field view these techniques as distinct alternatives, and for most projects, an early decision is made on which approach to use, with the rest of the modeling exercise then closely tied to that choice. It turns out that this decision is detrimental to the conceptualization and largely unnecessary as the event and state constructs can be brought together into a single, unified approach, expressly developed for HTA. This approach, DICE simulation, integrates much more flexible states (called "conditions" to distinguish them from the constrained Markov variety) with events that correspond to the happenings of interest.[4] In this overview, the features of DICE are presented in a question and answer format. A demonstration model is available for download as well.

General

What is DICE?

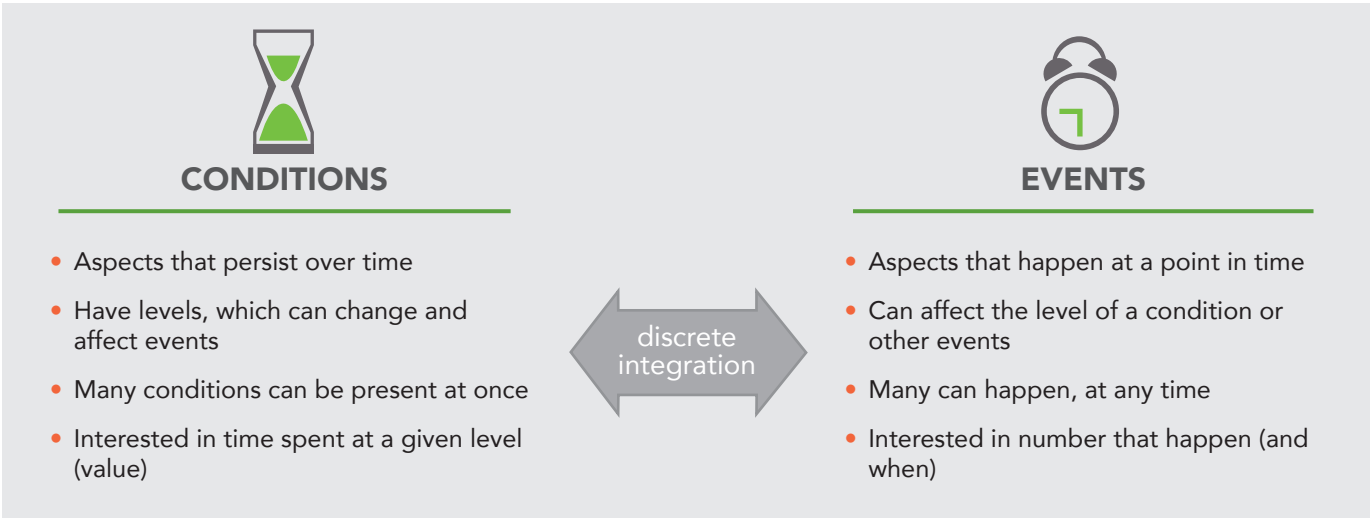
DICE stands for Discretely Integrated Condition Event simulation. It is a modeling technique specifically designed for decision-analytic modeling that conceptualizes a disease process and its management in terms of conditions and events.

Conditions

What are conditions?

Conditions are one of the two central features of DICE and represent any aspect of the problem that persists over time. Conditions have levels, which can change over time. A person can bear any number of conditions at the same time (e.g., age, body weight, glycemia, disease severity). The time spent in a condition can have value, measured in whatever units are of interest (utilities, quality of life score, costs, willingness-to-pay, weights for a multi-criteria decision analysis, etc.). This value may depend on the level of the condition.

Figure 1: The concepts that define a DICE



What can conditions be?

Conditions can characterize aspects of the disease (e.g., viral load, cancer stage, osteoporosis) or its consequences (e.g., renal impairment, pain, disability); features of the treatment (e.g., dose, compliance) or its unintended effects (e.g., neutropenia, weight change); or any other aspects that persist over time (e.g., costs, quality-adjusted life years [QALYs]). They can even pertain to the environment (e.g., analytic perspective, inflation rate, uptake).

Why "discretely integrated"?

Conditions can be changing continuously over time (e.g., tumor size, glycemia, body weight) but in a DICE these changes are evaluated at discrete points in time to avoid the mathematical complexity of simulating continuous interacting processes and to accord with our level of knowledge for most conditions, which is obtained at discrete time points. Thus, these conditions are integrated with (some of) the events, which are convenient time points for updating the conditions' levels.

Are conditions like Markov states?

A Markov state is a reduced form of a DICE condition. It is limited because a person can only be in one Markov state at a time, the state is static – it cannot change over time – and everyone in a state has to face the same consequences (i.e., transition probabilities). DICE conditions are not mutually exclusive and can evolve (e.g., viral load can decrease to below a threshold, stay below for some time and eventually rise above the threshold again; while CD4 count is increasing gradually; and other conditions, such as body weight, are changing as well). Thus, they provide much greater flexibility in representing the problem, without adding additional layers of complexity and leading to state explosion.

Are conditions like attributes in discrete event simulation?

A DICE condition is not restricted to information pertaining to an individual (e.g., the epidemic outbreak status in a given area is a DICE condition); any aspect that persists over time is represented as a condition. A DES attribute reflects any information that is personal to an entity.

Events

What are events?

Events are aspects of the problem that happen at a point in time. They have no duration but their time of occurrence is of interest. Events can happen at any time and several can occur simultaneously. Events can also have value, measured in whatever units are relevant (utility tariffs, quality-of-life score, costs, willingness-to-pay, etc.). This value may depend on when the event occurs, and on other factors such as the conditions that exist at that time.

What can events be?

Events can reflect what happens during the disease (e.g., progression of cancer, relapse, symptom relief, flare), or one of its consequences (e.g., fracture, death). Events can also represent aspects of the treatment (e.g., switch to another treatment, changes in dose or route of administration, start dialysis) or of its unintended effects (e.g., anaphylaxis, neutropenia). Events may also be used to reflect clinical activities (e.g., diagnostic testing, biopsy, surgery, admission to an emergency department or to hospital, discharge, admission to a nursing facility). Behaviors like non-compliance, stop smoking, work absenteeism, provide caregiving, and so on can be events.

Are events like Markov transitions?

A Markov transition can be represented as a DICE event (i.e., the event of transitioning from one state to another), but DICE events have many more features, including valuations such as costs and quality-of-life impacts, while Markov transitions are valueless. DICE events can even affect the entire context of the model (e.g., a new treatment entering the market). Moreover, they can occur at any point in time during the simulation (not just once during a cycle) and can coincide in time.

How do DICE events differ from DES events?

The events in a proper DES are occasions when one or more system variables change, whereas in DICE, events reflect what happens during the disease process and its management and the consequences can affect any aspect of the problem, not only the system variables.

Profiles

What are profiles?

A profile is a set of conditions that sufficiently characterizes a population of interest. Specific profiles are defined to represent the population adequately for the purpose at hand. Each profile denotes a "subgroup" of interest. Defining a single profile is tantamount to specifying a Markov cohort. There can be as many profiles as the analyst wants, including running all the profiles manifested in a particular population of patients (e.g., the participants in a clinical trial).

Is DICE an individual simulation?

Health economic analyses are always about a population specified by the user – never about individuals as such. The analyses for a population can be either deterministic or stochastic. If they are deterministic, it is convenient to consider the population as a cohort, while stochastic analyses require executing the model many times to fully reflect what happens in that population. Each replication does not, however, represent any particular individual – it is just one possible outcome in a population with the specified profile, but it has come to be known as "individual-level" simulation. DICE can run deterministic analyses; even a standard Markov model can be easily implemented with a single profile describing the cohort. Stochastic analyses following the Markov structure (so called "microsimulation") can be run as well as a time-to-event approach. DICE even has the flexibility to incorporate all three types of elements in a single model.

Using DICE

How is DICE specified?

A DICE simulation is specified using a set of tables that itemize all of the model's structure and workings. Only two sets of tables are required: one for Conditions and another for Events. An overall Events table lists all of the events, their initial time of occurrence and the name of their corresponding consequences table. This set of Tables is the full specification of the DICE simulation. In each Table, the applicable information is listed. For example, the table for an Event has a row for each consequence of that event and the columns contain the type of item affected (condition, event, output), the name of the item, and an expression that specifies what the consequence is. An Event can modify any of the Accumulators (e.g., QALYs) or Counters (e.g., is this event to be tallied); or even modify the model structure (e.g., acts as gate).

For the users' convenience and transparency, some of the specialized conditions can be put into their own tables; thus, there can be a Profiles table, and results can be stored in an Accumulators table if they are items that accrue (e.g., QALYs, costs) or in a Counters table if they are counted (e.g., hospitalizations, deaths, treatment switches).

Other helpful tabulations can list the features of the setting (e.g., discount rate) in a Context table, the particulars of a given analysis (e.g., time horizon) in a Scenario table, all the equations that may be used in an analysis in an Equations table. Other information needed for an analysis (e.g., equation intercepts, conversion factors) can go in a Constants table. Valuations (i.e., utilities, unit costs, etc.) can be specified in a Valuations table or can be incorporated directly into the Conditions and Events tables, as appropriate.

How does DICE work?

To execute a DICE, the selected software must read the Conditions table to establish the list of conditions to be considered during the simulation. Next, the Start Event table is read and its consequences are processed – each row in the table is an instruction that specifies a consequence. The occurrence of subsequent events is implemented by establishing an event schedule and maintaining it as events happen and conditions change. The consequences of each event are handled in the same way as for the Start Event.

What types of analyses can be done with DICE?

Since DICE can reflect any aspect of a disease and its management and apply whatever values matter, there is complete flexibility in terms of analyses - from the basic cost-consequences and budget-impact analyses, to cost effectiveness, cost utility, cost value, and even MCDA. These analyses can cover any period of interest, including lifetime. Any number of analytic types can be run simultaneously since they just require that the appropriate accumulators and counters be set up.

Table 1. Example of a Conditions Table

CONDITIONS		
Name	**Initial Value**	**Notes**
Sex	Pick from profile	
Age	Pick from profile	Depends on sex
Biomarker	Pick from profile	Distribution by age and sex
Utility		Select by age and sex
Current Treatment	Standard care	
Cancer Status	Remission	1=Remission 2=Progressed
Time Of Progression	Never	Never
Hazard ratio		Treatment Hazard Ratio

Table 2. Example of an Event Table (for a simple Start Event)

START EVENT			
Assignment Type	**Assigned Item**	**Expression**	**Notes**
Event	Progress	(-Ln (Rand ()/(0.000916* (if(Sex= "Female",-0.458,0)+Age*0.032 +Biomarker*0.003)))^(1/1.67)	Weibull using an embedded Cox proportional hazards
Condition	Utility	Vlookup(QoL,Age,Sex)	
Condition	Hazard Ratio	If(Tmt="New",0.42,1)	

Can DICE estimate QALYs?

In a DICE, QALYs are easily estimated. The accumulating QALY is a type of condition that accrues the time lived adjusted by its quality. Utility values are applied to any events that merit them and to the time spent in particular conditions, according to the level of the condition (as tariffs, percentage changes or whatever the analyst specifies).

What software is required?

There is no specific software requirement. The Tables specifying the DICE are conveniently entered on a spreadsheet (e.g., MS Excel®), and organized into corresponding worksheets. The handling of events is implemented using a very simple macro that reads each row in a Table and executes its instruction. This can be written as a Visual Basic for Applications (VBA) macro, thus keeping the entire DICE in Excel; or advantage can be taken of the tools provided in various simulation software that can accomplish these tasks efficiently. EviDICE™ is an Evidera tool that provides an efficient implementation of DICE in MS Excel, with built-in functions and other tools for the user.

How much time does a DICE model take to run?

The speed of the calculations depends on several factors, as well as the computer's processing capability – the choice of software, the complexity of the model structure, how many outcomes are to be produced, how uncertainty is handled, the number of profiles to be analyzed in a run, and whether the run is stochastic or deterministic. Running a single profile deterministically (i.e., similar to a cohort Markov model) is nearly instantaneous. By contrast, running in MS Excel a large quantity of profiles stochastically requiring complex calculations may take several minutes or even longer for the most elaborate

analyses. Carrying out probabilistic uncertainty analyses will add time proportional to whatever a single run takes. The best way of limiting run times is to carefully choose which profiles to run and keeping the number down. Compiling the discrete integrator macro increases the speed substantially.

How does someone use a DICE?

After carefully conceptualizing the problem, designing the model, obtaining the data and deriving the equations, the simulation is implemented as a DICE by specifying the Conditions and Events tables. Reviewers can inspect all the DICE tables and easily see what the DICE is doing. A user can modify the rows in any table to make the model pertinent to their setting and analysis of interest.

Use of a DICE can be facilitated by constructing a user-interface that assists the user in making changes and protects the integrity of the model and inputs. The user-interface makes it easy to run analyses, collect and display the results. This user-interface can be developed within the same Excel workbook that contains the DICE or it can be a separate piece of software, web interface, or tablet app.

Dissemination

How transparent is a DICE?

A DICE is as transparent as a model can possibly be. The entire specification is contained in the set of Tables. There is nothing hidden from the reviewer and the macro that executes the events is generic and easily inspected. There is no "black box" whatsoever. (Of course, if a modeler uses obscure inconsistent labeling and does not adhere to the prescribed table structure, the model can lose transparency).

Will authorities accept a DICE?

DICE meets all the stated modeling requirements of all HTA agencies at present. It can be transparently specified and implemented in a spreadsheet; it can accommodate any type of model that uses either conditions (e.g., Markov "states"), events (e.g., Markov "transitions") or both. DICE simulations are readily reviewed and even modified. The DICE method has been presented to many of the leading HTA agencies and no objections have been raised.

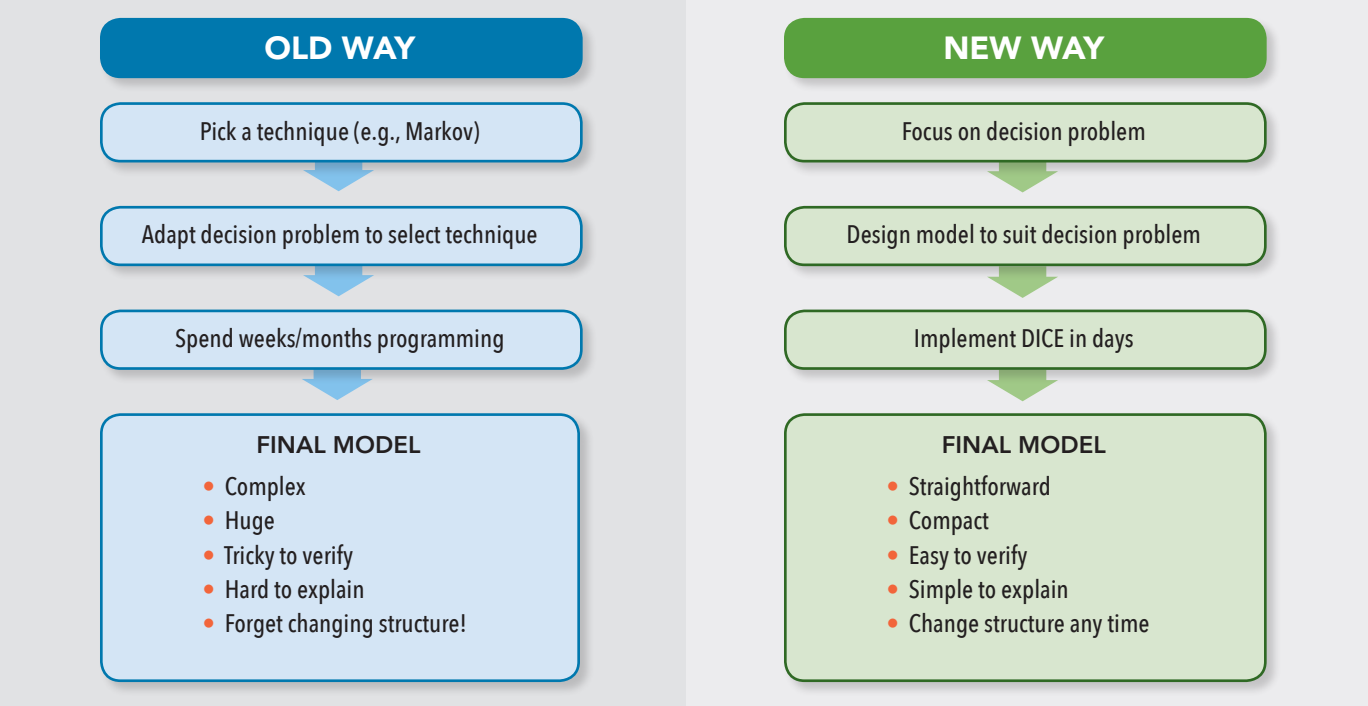
What is the experience with DICE?

Although the DICE specification is new (developed over the past two years), it is a formalization of techniques that draws from established methods that have been in use for more than 20 years (variously called semi-Markov, DES for HTA, etc.). Experience with it is growing rapidly as many companies are adopting it for disease models and health economic submissions.

Conclusion

The modeling techniques in use in our field today, even the relatively new discrete event simulation, date back to the 1950's and were developed to address different problems from those that face us today. They have not

Figure 2. DICE transforms the way we develop models



been updated to address evolving HTA requirements. DICE brings together the best of those techniques into a unified approach that is crystal clear, user friendly, and efficient. The two concepts (conditions, events) that define a DICE are straightforward and correspond directly to the disease and its management. Since DICE uses a standard framework, terminology, and a generic macro, users and reviewers need not "relearn" each new model. The disease-specific terms will change but the structuring and implementation remain consistent across models. The ability to fully program a DICE in familiar software (e.g., MS Excel) removes the need to purchase and learn new software and meets the requirement imposed by many agencies and other stakeholders. As the model is entirely specified by the Tables, there is no need to re-validate the macro (e.g., the VBA code in an MS Excel implementation) for each new model. Checking it once will suffice for all future models.

DICE is very easy to communicate and readily understood by clinicians, modelers, reviewers, decision makers, and other stakeholders. Even a person completely unfamiliar with modeling should be able to quickly understand the concept and review a model (the equations may require specialized statistical knowledge, but that is not specific to DICE). DICE simulation is very flexible. It can accommodate anything from very simple models to vast complex structures, all the while remaining very transparent and easy to debug. The technique does not introduce any awkward ideas (e.g., events represented as pre- and post-states) or impose unnecessary assumptions (e.g., memory-less states, single transitions per cycle).

DICE has been developed to meet the needs of the decision-analytic models commonly developed today. It is not meant for models that require explicit resources with capacities and queues (DES should be used in that case), nor for simulations that entail interactions with the environment or other people (agent-based should be used in that case). Nevertheless, it can be expected that DICE will transform how we develop models. DICE holds the promise of dispensing with the old way of modeling that starts with picking a technique, typically an oversimplified Markov, and forcing the decision problem to fit the technique, with one or more people spending weeks programming the model. Instead, research teams will focus on the decision problem, without wasting time thinking about the modeling technique, and designing a model that best fits the decision problem. This is possible because the DICE implementation is quick and straightforward so there is no need to worry about it from the beginning.

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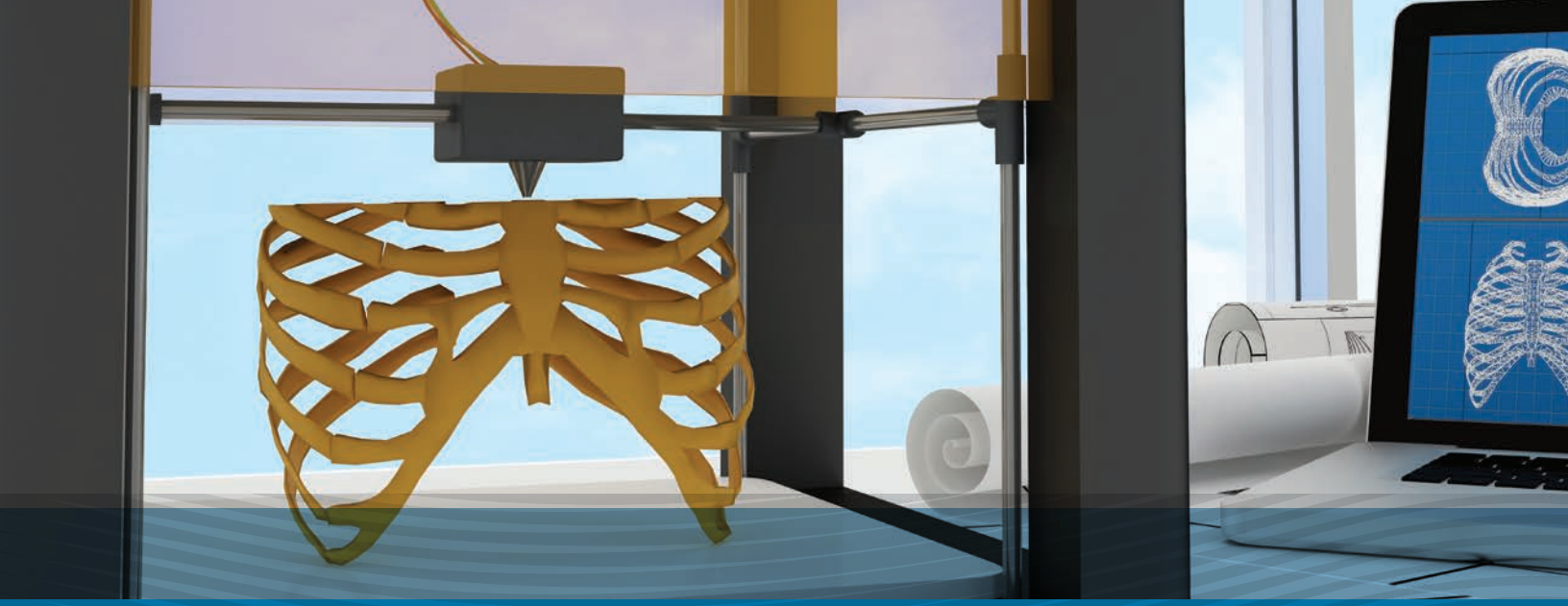


3D Printing is Revolutionizing the Medical Devices World, but are Payers Ready?

Ejegul Nuryyeva, MSc, Senior Consultant, Payer Strategy, Evidera

Ejegul Nuryyeva

Recent progress in healthcare applications of 3D printing is changing modern medicine in unprecedented ways. As an example, 3D printed implantable medical devices have the potential for significant innovation and clinical advantages in addressing unmet needs, such as:

- Creating customized implants fit for purpose and tailored to meet a patient's individual anatomy,[1] which can result in faster recovery time and less complications[2]
- Providing a more cost-effective alternative to current devices and implants[1] by being better adapted to individual patient needs
- Allowing surgeons to visualize deformity, plan, and prepare for surgery, in addition to reducing time spent on fitting the device during surgery[1,2]

However, 3D printed devices and implants also present an array of uncertainties and potential risks, including:

- Quality control in manufacturing[3] and consequent challenges for licensing and safety control
- 3D printed devices need to be produced fit for purpose and are likely to result in additional preparation time for patients and surgeons – conventional implants and devices are readily available[2]

So, how do we capture the value of the disruptive innovation of 3D printed medical devices for reimbursement? To understand the situation better, this article highlights the following questions.

- How are regulators evaluating 3D printed medical devices, and what impact may this have on how these devices enter the market?
- How are 3D printed devices evaluated from a reimbursement and market access perspective, and what are the implications for access considerations on overall market acceptance?
- What are the challenges from a market access perspective for new 3D printed medical implantable products, and what can device manufacturers do to address them?

To guide our answers, desk research and interviews with payers, surgeons, and industry experts in the U.S. and several European markets (France, Germany, Belgium, Sweden, Spain, and Switzerland) were conducted in late 2014 and early 2015.[2]

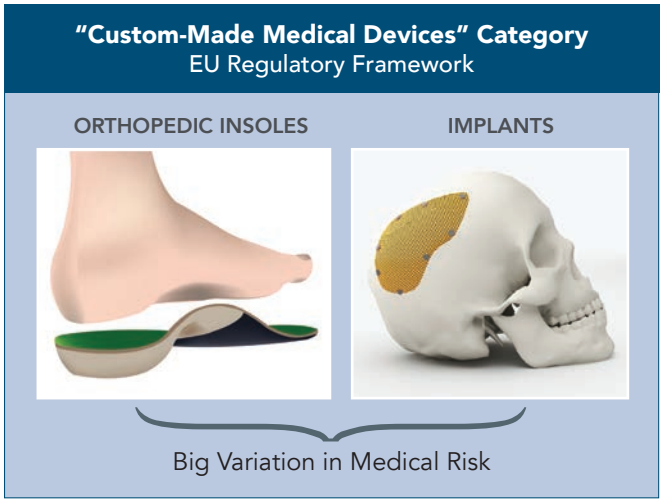
Where do regulators stand?

Europe - Regulation of 3D printed devices is not in the EU regulatory framework yet because regulatory burden is perceived to be "low"

"Manufacturers of medical devices for an individual patient, so-called 'custom-made devices', must ensure that their devices are safe and perform as intended, but their regulatory burden remains low." – *European Commission, 2012*[4]

Manufacturers, however, would like transparency and clarity around the regulation of 3D printed medical devices.

For example, Materialise, a provider of 3D printing software and services, points out that 3D printed medical devices are bundled under the same group as orthopaedic insoles.[5]



"Regulatory rules for orthopaedic insoles should be different from rules for 3D-printed surgical guides, implants and plates, since the latter will require more stringent quality requirements. For this reason, the very broad 'custom-made medical devices' category does not seem to accurately address the needs and potential risks of using 3D printing to design, produce and use patient-specific medical devices." – *Materialise, September 2014*[5]

Manufacturers should push for a clear EU regulatory guidance on 3D printed implantable devices so that patient safety is continuously ensured.

U.S. - Regulation of 3D printed medical devices is on the U.S. radar (FDA)

Currently, U.S. regulation of 3D printed devices is not significantly different from the regulation of conventional medical devices.[6]

"Not all devices or additive manufacturing technologies have the same risks or degrees of concern" – *FDA, October 2014*[3]

"We are regulating 3D printed devices the exact same way we regulate non-3D printed devices .... During the review process we have a few additional questions about how the manufacturing process could affect device performance. But right now there's no difference in regulation." – *Matthew Di Prima, a materials scientist with the FDA, Aug 2014*[6]

"What are going to be FDA's roles in looking at the controls for what would potentially be manufactured in a [healthcare] facility? On the shop floor, there may be one level of quality control, but in a medical institution, it may not be as well set up." – *Steven K. Pollack, director of the Office of Science & Engineering Labs at the FDA, June 2014*[7]

Manufacturers should use opportunities, such as public workshops on 3D devices, to collaborate with the FDA on the development of future 3D printing regulatory framework and to ensure that patient safety is preserved.

The U.S. Food and Drug Administration (FDA) recommends that 3D manufacturers schedule a pre-submission meeting to discuss the product with the FDA review team.[8] However, the rapid rise of 3D printing for medical applications raises a lot of questions. To address safety concerns, the FDA created a working group to assess technical considerations in 3D printing.[8] The first public workshop, titled "Additive Manufacturing of Medical Devices: An Interactive Discussion on the Technical Consideration of 3D Printing" was held October 8-9, 2014.[9] The goal of the workshop was for the FDA to better understand technical aspects of 3D printing technology, which will eventually contribute to how the regulatory landscape is established.

Are surgeons willing to drive uptake of 3D printed medical devices?

Where cost is less of an issue, "hassle factor," financial incentives, and P4P schemes may significantly affect the uptake of 3D printed medical devices for the mainstream patient[2]

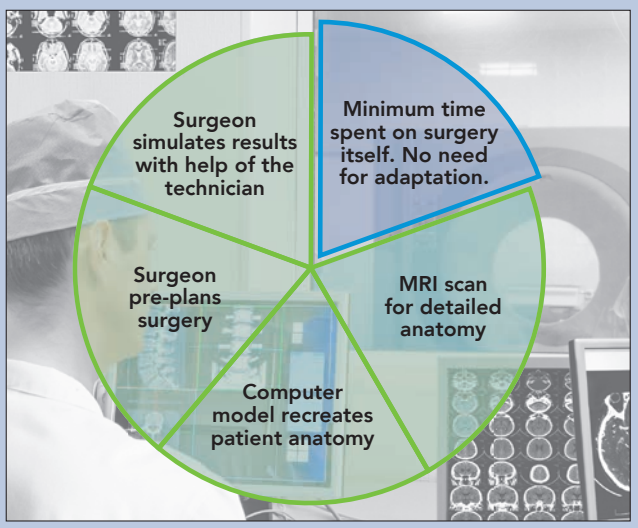
- The more complicated process may prevent mainstream use of 3D printed customized medical devices **(hassle factor)**
- For surgeons financially incentivized by operating on more patients, **impact of 3D on operating theatre efficiency** will be key
- **Pay-for-performance (P4P)** metrics may be another strong driver for the surgeon and for the hospital (e.g., for prestige and profitability reasons)

Whether it is challenges in reimbursement, incentive schemes, or the hassle factor, surgeons emphasize that they are more likely to use 3D printing technology only in special cases.[2]

With Standard Devices

If a patient requires a sophisticated surgery, fitting the device during the surgery may not be the most effective/easiest option due to possibility of poor fit, risk of complications, and more uncertainty in outcomes.

With 3D Printed Devices



With 3D printing technology, the majority of time is spent pre-planning the surgery.

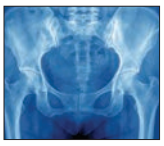
Time spent performing surgical procedure | Time spent on other activities (e.g., pre-planning)

Case Study in Hip Replacement

Patient populations for which surgeons would recommend reimbursement of 3D printed custom-made medical devices

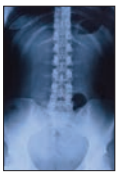
Hip Dysplasia

- Congenital or developmental deformation or misalignment of the hip joint
- Need for adapted devices (regular ones won't work)



Tumour (e.g., in pelvic bone)

- Need for adapted device to replace tumour area
- Surgeons appreciate a 3D anatomical model which gives a chance to visualize, plan surgery, and practice



Revision of Loosening

- Large amount of bone is lost because of revision, so having a custom device is a plus
- However, due to huge volume of this patient population, surgeons do not foresee widespread use in these cases

Private Sector

- Patients who can afford to pay for high cost of personalized medical devices

Last Resort

- When all other alternatives (e.g., pharmacotherapy, standard devices) are not (or no longer) an option

High risk of infections and/or complications

- Use of 3D printed custom-made device is likely to reduce surgery time, risk for complications, and recovery time

Applicable for a range of other disease areas

Are payers ready to pay more for the 3D printing revolution?

3D printing is not on payers' radar yet, as it is mostly reimbursed via DRG[2]

Payer

- Makes a decision whether to reimburse or not
- Can be a national, regional, or local payer (e.g., CFO, dept. head)

The majority of payers have not dealt (knowingly) with 3D printed devices.

Many payers mention they would not know if they are dealing with a 3D printed device (vs. device produced via regular manufacturing technique) because of the Diagnostics Related Groups (DRG) (i.e., bundled) method of payment.

"The first question we, payers, ask is 'Is it medically necessary?' The second question is 'Do we have a contract with you? Does patient's plan deny or allow payment out of network?' That being the case – whether you used the implant from one of the mainstream manufacturers like J&J or whether you do a homebrew 3D implant - we wouldn't know"
– Chief Medical Director at a major MCO, ***USA***

α

"When we get the bill for a service executed along a DRG, we don't know the costs divisions. We don't know which cost is for which process or device"
– Payer at a major sickness fund, ***Germany***

Surgeon

- Makes request for custom-made device
- Unlikely to be denied by payer if request does not break payer budget
- Advisory role on D&TC

There is "undiscovered need" for 3D printed devices amongst surgeon community.

"There is an undiscovered need for 3D printed medical devices, because a few of my colleagues are unaware of this. 3D printing companies need to be visible on congresses, but the best thing would be to have somebody like me, who has the experience of implanting 3D devices, to lecture to other surgeons. A lot of colleagues would be more impressed by having colleagues persuade them rather than sales reps."
– Surgeon at a public hospital, ***Sweden***

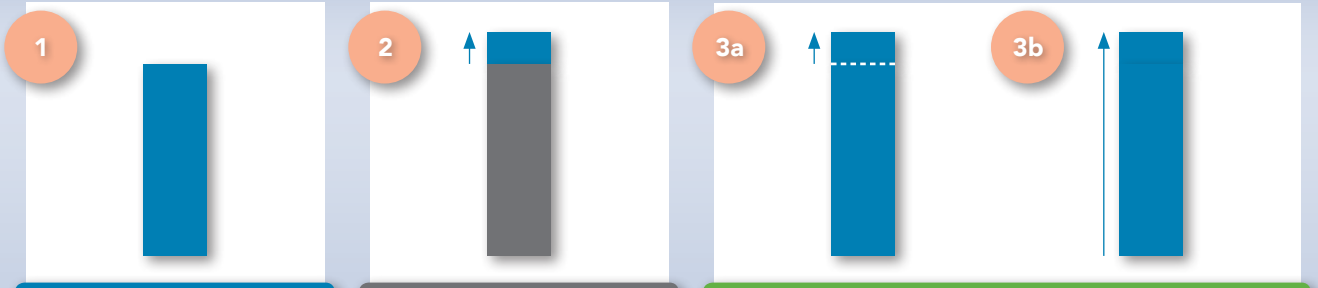
Having had a positive experience, surgeons expect that the demand for 3D printed devices will go up in the near future.

So far, surgeons have reserved requests for 3D printed medical devices only for special cases.

"If it is a desperate situation, we could accept a very high price for a 3D printed custom-made device. But if you start with a very high price, that's something I would need to negotite carefully with my boss. If there is another option that seems reasonable with a much lesser price, I would go for that option." *– Surgeon at a public hospital,* ***Sweden***

Potential DRG scenarios for a novel 3D printed medical device: another market access complication?[2]

Three potential scenarios for reimbursement of a new 3D printed medical device within the DRG system.



SCENARIO 1

A new product is used under the existing DRG

- There is no change to the tariff
- Cost of the product may or may not be depending on the size of the tariff and the cost of the product

SCENARIO 2

A new product is used under the existing DRG, but a supplementary payment covers the additional cost

- Hospitals may be able to apply for supplementary payments

SCENARIO 3

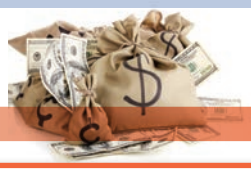
A The tariff of the existing DRG is uplifting to include additional funding to cover cost of new product

B A completely new DRG is created with sufficient tariff to cover cost of new product

Having a solid understanding on the reimbursement route of 3D printed devices will be key for reimbursement, optimal value proposition, and preparing the substantiating evidence.

3D printed medical devices with a higher price premium vs. conventional devices will face a higher degree of scrutiny.[2]

Level of price premium of 3D printed medical devices
(vs. conventional devices)



NONE/VERY LOW → HIGH

No HTA assessment

Bundled under existing DRG code

REASONS

1. No significant impact on budget
2. Assumption that 3D printed, custom-made device is better, hence better value for money vs. currently available options
3. Time constraints – payers have "other things to worry about"

"Normally [under 'expensive scenario'] you would need to first seek approval of the Director of Orthopedics service, and then persuade Economics Director of the Hospital and in some cases Pharmacy Services as well since they have wealth of knowledge in evaluating expensive analogues in pharma. However, if the values of 3D printed devices are not that high, then you would only need to get a good opinion from the Director of Orthopedics Department." – *Payer,* ***Spain***

HTA assessment

Evaluated as an "innovative device" with request for additional evidence (e.g., observational studies, etc.)

REASONS

1. High premium should be justified
2. Payers want to minimize impact on budget by potentially restricting the device to specific patient population or imposing other conditions on the manufacturer

"It is likely that we will see that AMNOG approach will be applied to the medical devices market soon. Due to the scandals we've seen in France and Germany with breast implants, politicians say that we need better quality control and implementation of added benefit rating. The question is 'When?' What that means for 3D printing companies is that they will need to submit a dossier to the G-BA in addition to getting a CE mark." – *Advisor to head of Doctor's Association (KV),* ***Germany***

Prioritizing next steps across markets for developing a comprehensive action plan for 3D printed devices

Regulation Clarity

- **Push for a clear EU Commission and FDA regulatory guidance** on 3D printed medical devices so that patient safety is continuously ensured; use opportunities, such as public workshops, to inform and collaborate

Price Exploration

- Understand **who pays? How do they pay? How are they paid?**
- Find out if DRG tariff allows for a premium over competitor implants
- Explore private sector and **ability to self-pay in certain markets**
- Consider **low-pricing strategy** for surgeons and payers to get them **accustomed** to 3D printing technology

Evidence Generation

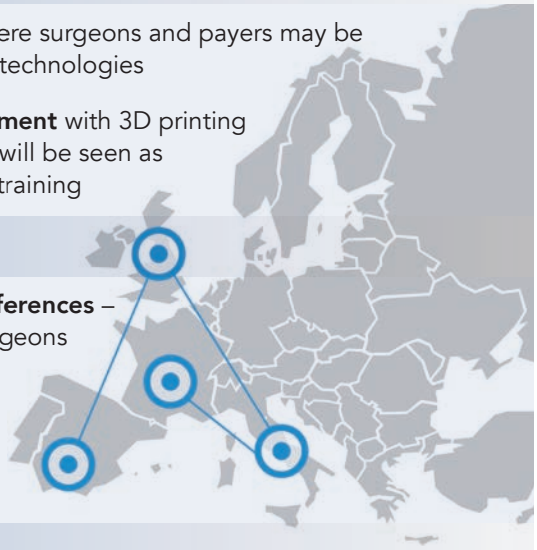
- Publish **observational studies** to provide additional information on safety and efficacy
- Consider inclusion of 3D printed devices into **registries** in countries such as Sweden where they are increasingly widespread and where there is a heightened worry about safety of new medical devices
- Consider inclusion in **guidelines** for specific sub-populations of patients where 3D printing technology is key to successful surgery and recovery

Value Proposition

- Don't underestimate the value proposition of additional services, such as providing cutting guides and models, which help surgeons to visualize the deformity and provide the ability to practice in advance of surgery

Launch Strategy

- Focus initial efforts on **reference centers** where surgeons and payers may be more open to experimenting with advanced technologies
- **Involve surgeons who are willing to experiment** with 3D printing technology and have them train others. This will be seen as more credible than having sales reps do the training



Informing stake-holders

- Create a **strong presence at important conferences** – present prolifically to get the attention of surgeons and health care providers
- **Inform payers, health care providers, and patients** on the benefits of 3D printing technology as it is likely to be new to them

Lessons Learned

1. There are many opportunities for 3D printing of specific medical devices (anything that benefits from customization)
2. Success will depend on balance between consolidated workload (pre- and during surgery) and safety aspects (wear and tear)
3. The commercial problem is the current lack of regulations for in-hospital printed devices, which threatens the 3D industry and the patient (as quality control cannot be on same level as industrial made)
4. Payer interests will depend on pricing of 3D printed device vs. medical devices printed via conventional techniques
   - from no interest if within same DRG
   - to high interest if with additional budget
   - or need for higher DRG
5. Key point to find out is cost effectiveness (or efficiency) of 3D printed medical devices versus standard devices, e.g., impact on direct medical cost and length of surgery

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ACKNOWLEDGEMENT

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Closing the Gap: Early Access and Uncertainty

The Preparation Earmark, The Choice of Analytical Tools, and Data Needs

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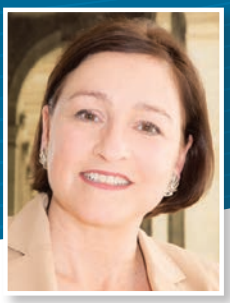

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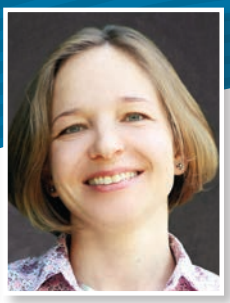


Agnes Benedict

Increasing uncertainty with early access

Uncertainty is always part of the drug development process, with limited clinical knowledge and a changing environment in both the treatment and payer landscapes. Delivering a molecule as early as possible to patients further limits the opportunities to collect information, emphasizing the importance of assessing, addressing, and planning for uncertainties. Hence, using the right analytical tools is crucial. These should help identify and assess the importance of these uncertainties, allowing attention to be focused on evidence substantiating the most essential patient benefit.

At the same time, the external environment into which drugs are launched is also changing. Healthcare reforms are initiated and implemented in far less time than it takes to develop a pharmaceutical asset; the emphasis on value is increasing, and competitors are equally seeking an earlier and earlier launch. Thus the discussions on value development plans need to be framed by the limited information of the clinical benefit (e.g., mature data on the outcome of interest, such as overall survival) and the future payer requirements, focusing on a more integrated approach to convey value and differentiation, and to align on a value proposition that can be substantiated to meet potential pricing and reimbursement requirements.

New market access approaches aiming to deliver earlier access, such as conditional marketing authorization as seen in Medicines Adaptive Pathways to Patients (MAPPs), are shifting the focus not only on a more integrated approach of licencing and pricing and reimbursement (P&R), but also on the uncertainties and flexibility in the face of the continuously developing evidence base. Adaptive market access should be based on adaptive evidence development and flexible tools incorporating the changing evidence base.

The need for uncertainty management is not new

When anticipating P&R outcomes in the development process of new pharmaceutical products, the sources of uncertainty can be identified and managed, depending on the complexity of the molecule and the level of incongruity of the environment. Appropriate analytical forecasting tools can be used to identify the best course of action to narrow uncertainty, and actions can be determined, such as missing data can be collected according to existing and anticipated payer requirements.

A critical factor in the management of uncertainty is the time involved in the development of a molecule from Phase 1 to completion of Phase 3. Potential sources for uncertainty can be monitored and assessed during that time. However, if a molecule is developed via an expedited process (e.g., launch and market access at Phase 2 or earlier), it is confronted with a triple challenge in managing uncertainty: less time to identify and plan for uncertainties, new uncertainties due to incomplete data, and the need for new, innovative tools and pathways to manage these uncertainties.

Different situations imply different levels of uncertainty in the development process. In the case of an indication with limited competitors on the market for the targeted population, or line of therapy, and no new competing developments under way, there is limited incentive for earlier access. Thus, the development of the standard clinical plan can be completed. Nevertheless, there may still be uncertainty about the price potential of the molecule, and unexpected changes may still happen in the health policy environment.

In other situations, the molecule may be developed in parallel with competitors, racing for first-in-class status. In this case, reducing the time spent in development and applying for early access opportunities can be crucial. This can result in a shorter development process, potentially less conclusive data on patient relevant endpoints, and a not fully conclusive safety profile, increasing the uncertainty in both clinical and health economic value stories. Since this is increasingly prevalent in advanced oncology, a short example showing the potential sources of uncertainty in the data and the currently used solutions are described below.

Sources of uncertainty

Turning towards early access limits the time and the resources for collecting data. In oncology, this often manifests through the use of Phase 2 trial data, a shorter follow-up period, use of surrogate outcomes, and reduced potential for data collection outside the clinical trial program, leading to immature data, cross-over designs, single arm trials, limited comparators, and lack of quality of life (QoL) data (see Figure 1). This limited data, though increasing uncertainty, does not necessarily affect the decision making.

Figure 1. Trial design situations for early regulatory access create uncertainty and significant challenges for health technology assessment (HTA) and pricing and reimbursement

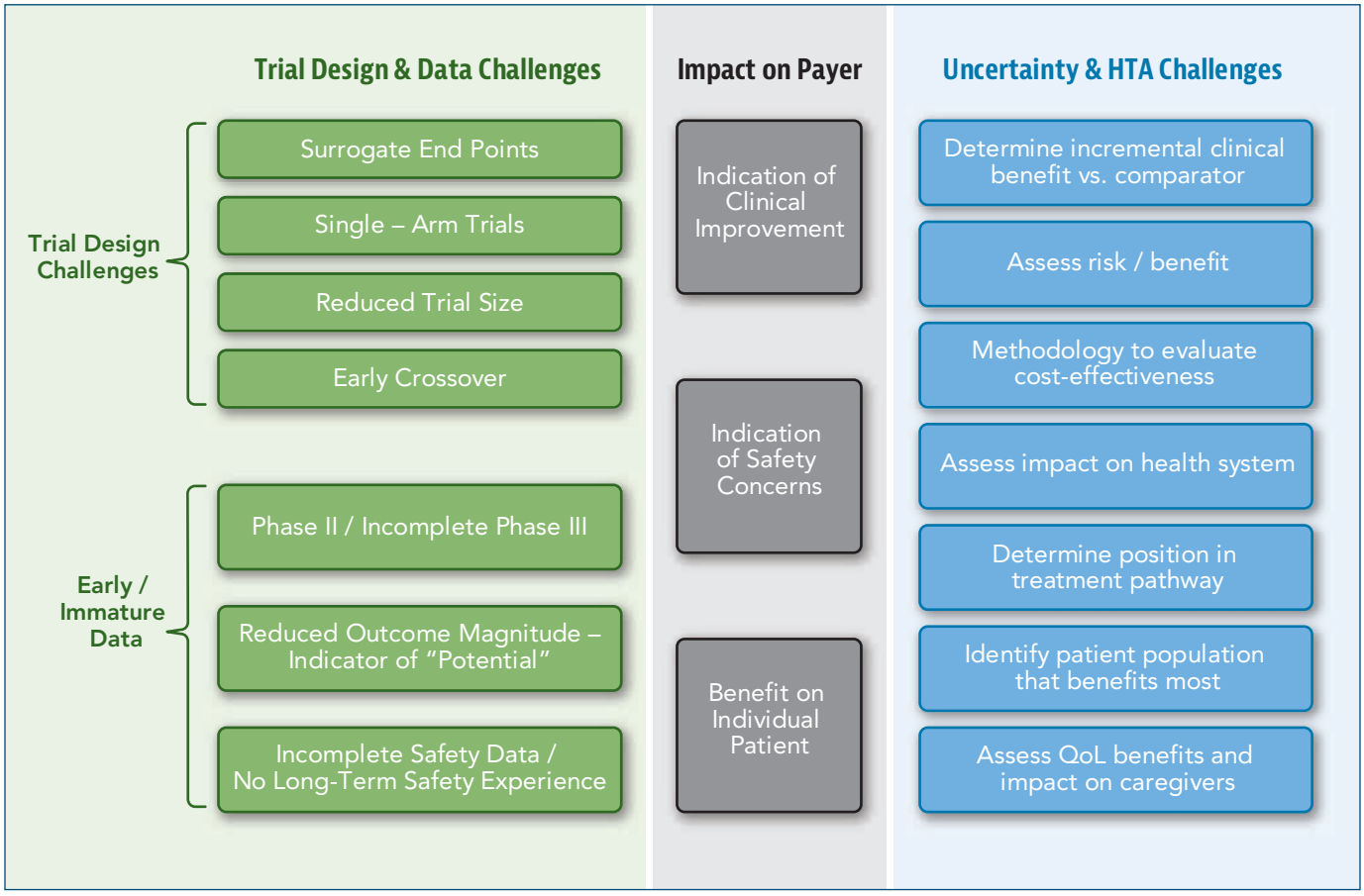


Table 1. Oncology technology appraisals by NICE after conditional marketing authorization

Brand Name	Generic Name	Therapeutic Area	HTA Number	Duration (Months)
Votrient	Pazopanib	Renal Cell Carcinoma	TA215[1]	~10
Xalkori	Crizotinib	Lung Cancer	TA296[2]	~9
Bosulif	Bosutinib	Chronic Myelogenous Leukemia	TA299[3]	~ 8.5
Pixuvri	Pixantrone	Non-Hodgkin's Lymphoma	TA306[4]	~ 27
Pomalyst	Pomalidomide	Multiple Myeloma	TA338[5]	~8.5
Zydelig	Idelalisib	Chronic Lymphocytic Leukemia	TA359[6]	~10

In the UK, the National Institute for Health and Care Excellence (NICE) has evaluated six drugs to date after conditional marketing authorization (see Table 1). As NICE has the most complete documentation of the appraisal submissions and review documents, these were reviewed to assess the sources of uncertainty mentioned in the descriptions of the appraisal and the decision.

As expected, these highlight that, in the face of limited clinical evidence, the greatest uncertainty in the oncology health technology assessments is presented by the estimation of progression-free survival (PFS), overall survival (OS), and the relative treatment effect. In the assessment documentation, treatment duration was also indicated to have high levels of uncertainty in half of the assessments (3 out of 6) (see Figure 1). In all cases, the uncertainty of relative effectiveness was emphasized as contributing to the decision making, with the uncertainty of PFS/OS estimates following closely behind. In the majority of cases, the decision was driven mostly by these two estimates, balancing the cost-effectiveness by reduction in costs through patient access schemes. Based on the documents, there were no extra stipulations or allowances for early access drugs, allowing the assumption that the same criteria and expectations are used as with drugs with fully executed development programs.

Levels of uncertainty

Even the most uncertain business environments contain a lot of strategically relevant information. First, it is often possible to identify clear trends or learnings from previous assessments of molecules that underwent early access or faced a similar situation that can help identify potential payers' expectations. Second, there is usually a large amount of information that may not be currently evaluated but can be assessed with the appropriate analyses.[7] Good examples could be the implicit assessment criteria for early access molecules or long-term survival in a disease area where the clinical trials were short-term and terminated early. Appropriate analysis may reveal important insights, and the level of uncertainty may be shifted to a manageable degree.

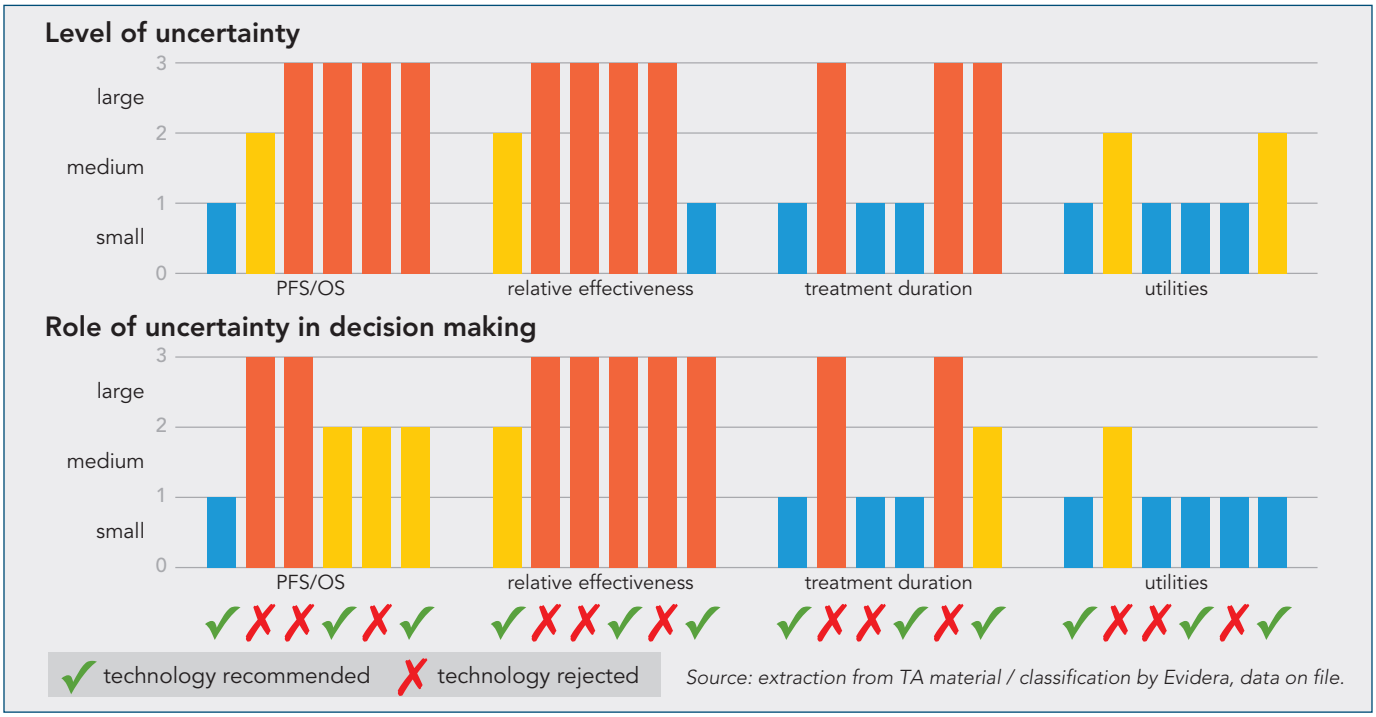
The uncertainty that remains after the best possible analyses have been done is, what Courtney calls, residual uncertainty[7], such as the outcome of an ongoing payer debate on modifying assessment or value criteria. Courtney, et al., argue that even these residual uncertainties are not so uncertain and fall into four broad levels according to their relevance to strategic decision making.

- Level 1: A Clear-Enough Future
- Level 2: Alternative Futures
- Level 3: A Range of Futures
- Level 4: True Ambiguity

Market access situations can also be categorized into these four levels, and a potential course of action can be selected according to this categorization. In the following section, we demonstrate each with an example of a potential situation for an early access molecule.

The mitigation strategies for level 2 and 3 uncertainty around the long-term overall survival – not only for the treatment of interest, but also, for relative effectiveness versus the comparator(s) – require extensive statistical analyses of the trial data. Supplementing trial data by

Figure 2. Level of uncertainty of key parameters and their role in decision-making among oncology technology appraisals by NICE after conditional marketing authorization



Summary of Approaches: Level 1 – A Clear-Enough Future

"At level 1, managers can develop a single forecast of the future that is precise enough for strategy development. Although it will be inexact to the degree that all business environments are inherently uncertain, the forecast will be sufficiently narrow to point to a single strategic direction. In other words, at level 1, the residual uncertainty is irrelevant to making strategic decisions.[7]"

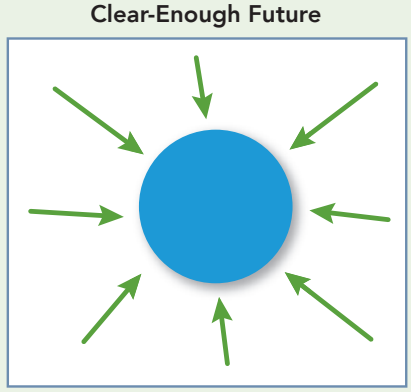


Table 2. Example for Level 1 residual uncertainty – A Clear-Enough Future

A hypothetical situation	Molecule performance outcomes and evidence of meeting payer assessment criteria are available; market is well defined with very few competitors; and, therefore, the price potential is predictable within margins and competitor performance. Risk sharing and patient access schemes can be planned.
Analytic tools	Forecast can help determine the price that will maximize the chances of market access
Examples	Orphan molecules (for the time being) with few competitors; later lines in oncology with OS data (excluding non-immuno-oncology molecules)
Applicable to early access molecules	Not really, as it requires sufficient information from full clinical development programs
Payer requirements for P&R known	Yes

Summary of Approaches: Level 2 – Alternative Futures

"At level 2, future can be described as one of a few alternate outcomes, or discrete scenarios. Analysis cannot identify which outcome will occur, although it may help establish probabilities. Most important, some, if not all, elements of the strategy would change if the outcome were predictable. In another common level 2 situation, the value of a strategy depends mainly on competitors' strategies, and those cannot yet be observed or predicted.[7]"

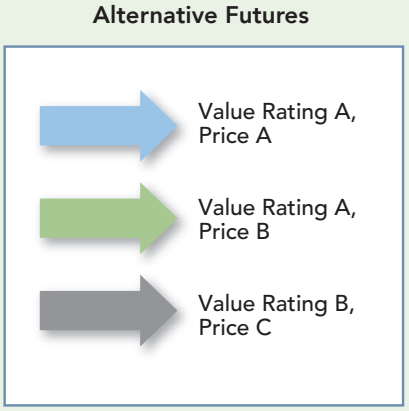


Table 3. Example for Level 2 residual uncertainty – Alternative Futures

A hypothetical situation	Early regulatory approval; conditional marketing authorization (CMA). Molecule performance outcomes at Phase 2 are insufficient; further data collection is required to be correlated to payer assessment criteria; therefore, depending on the expectation on the future data, price potential can include several options. Contracting, risk sharing and patient access schemes can be planned for if performance outcomes do not meet payer requirements or thresholds.	
Analytic tools and mitigation options	**Decision tools** • Decision analysis / decision trees, per and across markets • Option valuation • Game theory	**Data tools** Aim is to align existing data to payer requirements and concentrate on patient benefit evidence gaps using one of the following: • Clinical trial simulations • Adaptive trial design • Analyses of existing databases • PFS can be supported by other patient relevant endpoints, e.g., by demonstrating causality of patient benefits to adverse event (AE) improvement, QoL, etc. • Enriched populations Time-limited HTA decision / pricing needs to be aligned to assess future performance evidence and price potential. Table 4 provides examples used in the NICE appraisals of drugs after CMA.
Examples	Oncology molecules with PFS or objective response rate (ORR) endpoints with immature or no OS data, or molecules using other surrogate endpoints where correlation with final outcome has not been established; here further long term OS data is required to be collected. Market access is achievable, price is in question.	
Applicable to early access molecules	Yes	
Payer requirements for P&R known	Not clear, however can be assessed and some information collated based on available evidence.	

Table 4. Examples of molecules with CMA that present "Level 2 and 3 uncertainty"

Oncology domain	Indication	Orphan	Year	Primary Endpoints	Source of Uncertainty	Mitigation strategy in UK HTA submission and result
Haematology	Treatment of CML in patients previously treated with ≥1 TKI	YES	2013	Cytogenic Response	No head-to-head data; long term OS benefit, both the treatment and the comparators; therefore relative effectiveness too. PFS and OS were very immature (25.0%, 19%) – while the duration of the extrapolation was 48 years	Attempt was made to use surrogate outcome, but was not successful. Assumption on post-treatment gain was not accepted.
	Lymphoma (Hodgkin's, CD30-positive)	YES	2014	Survival	N/A	N/A
	Non-Hodgkin's lymphoma when other treatments are no longer working	NO	2012	Response Rate (Complete Remission)	Long-term OS. Only 61% dead at end of trial, extrapolation need is 18 years.	Extensive statistical analyses of the data; conservative assumption on post-progression OS gain. Arguments accepted after appeal.
Thyroid cancer	Progressive, unresectable, locally advanced, or metastatic medullary thyroid carcinoma	YES	2014	Progression Free Survival	N/A	N/A
	Advanced medullary thyroid cancer	NO	2012	Progression Free Survival	N/A	N/A
Lung Cancer	Non-small-cell lung carcinoma	NO	2012	Progression Free Survival	Long-term OS uncertain for comparator due to cross-over. Extrapolation was for 13.1 years, with 65%, 28% progressed or dead.	Mitigation was done using external data, KOLs, cross-over adjustment, and network meta-analyses.
Skin Cancer	Advanced basal-cell carcinoma	NO	2013	Response Rate (CR - Complete Response, PR – Partial Response)	N/A	N/A

(Resources used for content in this table are available upon request.)

Summary of Approaches: Level 3 – A Range of Futures

"At level 3, a range of potential futures can be identified. That range is defined by a limited number of key variables, but the actual outcome may lie anywhere along a continuum bounded by that range. There are no natural discrete scenarios. As in level 2, some, and possibly all, elements of the strategy would change if the outcomes were predictable.[7]"

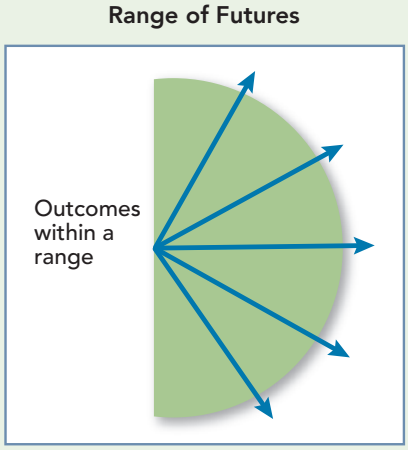


Table 5. Example for Level 3 residual uncertainty – Range of Futures

A hypothetical situation	Adaptive Pathways. Molecule performance outcomes at Phase 2 are available but do not - or only partially - meet payer expectations, due to the limitations in data (such as surrogate outcome and early cross-over), substantial post-hoc analyses and various assumptions are required; therefore price potential can be aligned to a range of possible value assessment outcomes and strongly aligned to competitor developments. Contracting, risk sharing, and patient access schemes can be planned only with difficulty because of data uncertainty.	
Analytic tools and mitigation options	**Decision tools** • Scenario planning across markets • Latent demand research – repeated over time with payers	**Data tools** Aim is to align existing data to payer requirements and concentrate on patient benefit evidence gaps. • Validation of surrogate outcomes • Use of external data to support patient benefit and relative effectiveness • Enriched populations • Analyses of existing databases • PFS can be supported by other patient relevant endpoints, e.g., by demonstrating causality of patient benefits to AE improvement, QoL, etc. Time-limited HTA decision / pricing has to be aligned to assess future performance evidence and price potential.
Examples	Oncology molecules launched with adaptive pathways and with limited data due to, for example, PFS or ORR as primary endpoints, cross-over design or incomplete trials. Market access may be thwarted by lack of mature data.	
Applicable to early access molecules	Yes	
Payer requirements for P&R known	Not clear, however can be assessed and some information collated based on available evidence	

Summary of Approaches: Level 4 – True Ambiguity

"At level 4, multiple dimensions of uncertainty interact to create an environment that is virtually impossible to predict. Unlike in level 3 situations, the range of potential outcomes cannot be identified, let alone scenarios within that range. It might not even be possible to identify, much less predict, all the relevant variables that will define the future.

Level 4 situations are quite rare and they tend to migrate toward one of the other levels over time.[7]"

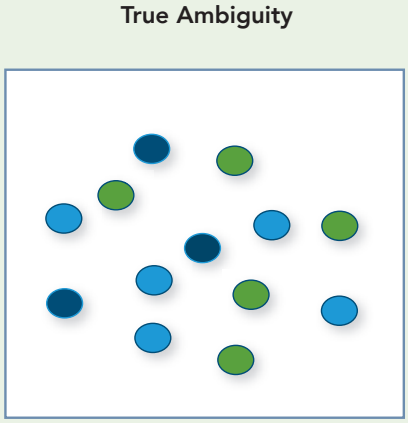


Table 6. Example for Level 4 residual uncertainty – True Ambiguity

A hypothetical situation	No basis to forecast any outcome
Analytic tools	Pattern recognition
Examples	Potentially gene therapies or completely new mechanisms / technologies that may require specific evidence substantiation
Applicable to early access molecules	Not really, but may apply to other new developments such as cure in gene therapy
Payer requirements for P&R known	Yes, as current requirements for "regular" molecules are known, but difficult to apply to gene therapies.

obtaining and analyzing external data (see Table 4 for examples) is a very important, additional mitigation option.

However, the different techniques / methods not only help to reduce the uncertainty, they also bring their own inherent uncertainty. For example, extrapolation of trial data can quantify the alternative results and can determine the most likely ones, but it can be an important source of uncertainty and will point to a very wide range of alternative results, some of which may not be favourable. This uncertainty increases with larger time period without data. For molecules with early access options, due to the limited data, long-term outcomes such as OS, can be the main source of uncertainty. This can be seen in two cases among the NICE assessments with CMA (see Table 4).

Lack of information on the relative effectiveness is another main source of uncertainty (see Figure 2). Some of the mitigation techniques include conducting network meta-analyses, or simulated treatment comparisons, or matching adjusted indirect comparisons.[8] Depending on the level and type of information in the public domain about competitors, level of uncertainty can result in either a few alternative scenarios or a wide range of options.

Summary

Early development molecules face a range of uncertainties. These can be driven by uncertainty of the data, the clinical and payer environments, such as unrevealed expectations from payers on how to assess and manage patient benefit expectations, and competitor developments. To consider and move forward with early access, it is critical that companies understand:

1. which uncertainty factors can in fact be known at least to some extent (such as payer expectations and application of HTA requirements),
2. which factors are influential in the decision making process, and
3. the techniques that can be used to mitigate this uncertainty.

For example, in oncology, critical data on which to focus include long-term clinical outcomes, relative treatment effects, and relative benefits in health related-quality of life, as well as information such as length of treatment, that helps assessment of true costs associated with a new molecule. Choice of the appropriate analytical tools and their systematic alignment with a broad-based set of data can greatly support early access.

This can act as part of the foundation of early formulation of the potential value messages. As most uncertainties require complex strategies that focus on both the data and the clinical and payer environments, it is equally critical to align all members of the development team to the early clinical value and patient benefit of a molecule that aims to launch with early, such as Phase 2, data.

For more information, please contact Susanne.Michel@evidera.com, Noemi.Muszbek@evidera.com, or Agnes.Benedict@evidera.com.

REFERENCES

[1] Pazopanib for the First-Line Treatment of Advanced Renal Cell Carcinoma. NICE Technology Appraisal Guidance [TA215]. 23 February 2011. Available at: https://www.nice.org.uk/guidance/ta215. Accessed April 19, 2016.

[2] Crizotinib for Previsouly Treated Non-Small-Cell Lung Cancer Associated with and Anaplastic Lymphoma Kinase Fusion Gene. NICE Technology Appraisal Guidance [TA296]. 25 September 2013. Available at: https://www.nice.org.uk/guidance/ta296. Accessed April 19, 2016.

[3] Bosutinib for Previsously Treated Chronic Myeloid Leukaemia. NICE Technology Appraisal Guidance [TA299]. 27 November 2013. Available at: http://www.nice.org.uk/guidance/ta299. Accessed April 19, 2016.

[4] Pixantrone Monotherapy for Treating Multiply Relapsed for Refractory Aggressive Non-Hodgkin's B-Cell Lymphoma. NICE Technology Appraisal Guidance [TA306]. 26 February 2014. Available at: http://www.nice.org.uk/guidance/ta306. Accessed April 19, 2016.

[5] Pomalidomide for Relapsed and Refractory Multiple Myeloma Previously Treated with Lenalidomide and Bortezomib. NICE Technology Appraisal Guidance [TA338]. 25 March 2015. Available at: https://www.nice.org.uk/guidance/ta338. Accessed April 19, 2016.

[6] Idelalisib for Treating Chronic Lymphocytic Leukaemia. NICE Technology Appraisal Guidance [TA359]. 28 October 2015. Available at: https://www.nice.org.uk/guidance/ta359. Accessed April 19, 2016.

[7] Courtney H, Kirkland J, Viguerie P. Strategy Under Uncertainty. Harvard Business Review. Nov-Dec 1997. Available at: https://hbr.org/1997/11/strategy-under-uncertainty. Accessed April 15, 2016.

[8] Ishak KJ, Proskorovsky I, Benedict A. Simulation and Matching-Based Approaches for Indirect Comparison of Treatments. *Pharmacoeconomics.* 2015 Jun;33(6):537-49. doi: 10.1007/s40273-015-0271-1.

Evidera Presents at ISPOR's 21ST Annual International Meeting

MAY 21 – 25, 2016 – WASHINGTON, DC, USA

SHORT COURSES

Sun., May 22, 8:00 AM - 12:00 PM

Discrete Event Simulation for Economic Analyses – Concepts

Instructors: Caro JJ, Moller J

Sun., May 22, 1:00 - 5:00 PM

Discrete Event Simulation for Economic Analyses – Applications

Instructors: Caro JJ, Moller J

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

Instructors: Marsh K, IJzerman MJ, Devlin N, Hummel M, Garau M, **Sri Bhashyam S**

WORKSHOPS

SESSION III
Tues., May 24, 5:00 - 6:00 PM

W18: Predicting Market Outlook: Enhancing Market Forecasting Via Application of Pharmacoeconomic Modeling Techniques

Discussion Leaders: Deniz B, Stern S, Peterson S

W19: Patient-Centered Benefit-Risk Analysis: Regulatory Developments and Prospects

Discussion Leaders: Luce B, Ho M, Gerson J, Eggers S

SESSION IV
Wed., May 25, 1:45 - 2:45 PM

W26: Patients as Partners in the Development and Interpretation of Clinical Outcome Assessments: Methods, Challenges and Benefits

Discussion Leaders: Anatchkova MD, Mullin TM, Deal LS, Bast A

ISSUE PANELS

SESSION I
Mon., May 23, 11:00 AM - 12:00 PM

IP2: Are We Ready for a Cure? Key Value Demonstration and Policy Considerations for the New Wave of Potentially Curative Therapies

Moderator: Faulkner E
Panelists: Thomas SK, Syrek-Jensen T, Daniel GW

SESSION III
Tues., May 24, 2:15 - 3:15 PM

IP12: Multi-Criteria Decision Analysis: A New Paradigm in Health Care Decision Making? What are the Current Status, Challenges, and Opportunities?

Moderator: Thokala P
Panelists: Marsh K, Goetghebeur MM, Castro H

ISPOR FORUMS

SESSION I
Mon., May 23, 6:15 - 7:15 PM

F2: Clinical Outcomes Assessment (COA) Measurement in Rare Disease Clinical Trials - a Case Study on Application of Emerging Good Practices

Moderator: Benjamin K
Speakers: Burke L, Patrick DL, **Vernon MK**

POSTERS

SESSION I
Mon., May 23, 8:30 AM - 2:15 PM

PCV52: Clinical Events Avoided with Apixaban Compared to Edoxaban for the Initial Treatment and Prevention of Venous Thromboembolism

Lanitis T, Hamilton M, **Quon P, Browne C**, Cohen A

PCV69: How do Utilities Vary for Cardiovascular Events? A Systematic Review

Blieden M, Szatkowski A, Cheng L, Paoli CJ, Gandra SR

SESSION II
Mon., May 23, 3:45 - 7:45 PM

PRM9: Model Observational Bridging Study on the Effectiveness of Ezetimibe on Cardiovascular Outcomes

Ferrieres J, Dallongeville J, **Getsios D**, Rossignol M, Abenhaim L, Grimaldi-Bensouda L, Amzal B

PRM22: Establishing Equivalence of Electronic Clinician-Reported Outcome Measures

Feaster T, Fuller R, McNamara CW, **Lenderking WR**, Miller DS, Sabatino D, Butler A

PRM80: Improving Precision by Applying Disease Progression Equations from Multiple Sources in the Alzheimer's Disease Archimedes Condition Event (ACE) Simulator

Tafazzoli A, Dos Santos R, Ishak J, Krotneva M, Kansal A

PRM82: The Evolution of Economic Modeling in Alzheimer's Disease: Where Do We Go From Here?

Hernandez L

PRM84: Structural Sensitivity Analyses of Mortality and Location of Care in a Simulation of Alzheimer's Disease

Kansal A, Dos Santos R, Tafazzoli A

PRM115: Psychometric Evaluation of the Functional Assessment of Cancer Therapy-Anemia (FACT-AN) in Dialysis and Non-Dialysis Patients with Anemia Associated with Chronic Kidney Disease

van Nooten FE, **Wiklund I**, Trundell D, Cella D

PRM118: Qualitative Equivalence between Paper and Electronic Tablet Versions and Usability of 12 Patient-Reported Outcome Instruments for Rheumatoid Arthritis

Eremenco S, Stringer S, Gleeson S, Landrian A, Falcon I

PRM132: Qualitative Interviews versus Social Media Searches: Comparing Two Approaches for Concept Elicitation

Gelhorn HL, Anand SB, Parvizi J, Morrison T, Yu H, **Pokrzywinski R, Al-Jassar G, Cox A**, Dashiell-Aje E, Chen AF

PRM143: Developing a Patient-Reported Outcome Measure for Patients with 4 Subtypes of Soft Tissue Sarcoma

Skalicky AM, Ghate SR, Perez JR, **Rentz A**

PRM196: Indirect Treatment Comparisons with Guided Matching-Based Adjustment: A Hybrid of the STC and MAIC Techniques

Ishak KJ, Rael M, Proskorovsky I

PRM203: To Join or Not To Join? Analysis of Progression-Free and Overall Survival Using Multi-State Modeling

Rael M, Ishak KJ, Benedict A

SESSION III
Tues., May 24, 8:30 AM - 2:15 PM

PIH32: Health-Related Productivity Losses Due to Endometriosis in the United States: Evidence from a Cross-Sectional Survey

Soliman AM, Castelli-Haley J, **Coyne K**, Winkel C

PIH33: Examining Health-Related Productivity Losses Due to Uterine Fibroids (UF) in the United States (US) Using the Health-Related Productivity Questionnaire (HRPQ)

Soliman AM, Castelli-Haley J, Snabes MC, Owens CD, **Coyne KS**

SESSION IV
Tues., May 24, 3:45 - 7:45 PM

PDB37: Modeling Cardiovascular Outcomes of Treatment with Empagliflozin in Type 2 Diabetes Based on Hard Outcomes Data

Kansal A, Zheng Y, **Proskorovsky I, Krotneva S**, Kandaswamy P, Ruffolo A

PDB68: Patient Perceptions of Non-Insulin Injection Devices for Type 2 Diabetes

Matza LS, Stewart KD, Paczkowski R, **Murray L, Landrian A**, Boye KS

PIN18: Cost-Consequences Analysis of Coformulated Elvitegravir, Cobicistat, Emtricitabine, and Tenofovir Alafenamide in Patient Populations with Differing Risk Profiles

Gallant J, Altice F, **Folse H**

PIN52: Evaluation of the Performance Properties of the Influenza Patient-Reported Outcomes Instrument (FLU-PRO)

Powers JH, **Bacci ED, Leidy NK, Stringer S, Kim K**, Memoli MJ, et al

SESSION V
Wed., May 25, 8:30 AM - 2:45 PM

PHP33: Surrogate Endpoints - Can Pricing and Reimbursement Align Across Markets - Or Will the Same Outcome Continue To Be Rewarded Differently for Pricing and Reimbursement?

Chang E, Satherley A, Awasthy S, Michel S

PHP152: Self-Perception of Aging: Results from a Global Survey Assessing the Psychosocial Impact of Facial Aging

Bassel M, Gallagher CJ, **Kawata AK**, Hanson KA

PMD3: Clinical Utility of Early Multigene Genetic Testing in Pediatric Patients with Suspected Seizure Disorders and Syndromic Epilepsies

Faulkner E, Spinner DS, Cardeiro D, Stanley CM, Foss TR, Zare AS, Boles RG, Le NM

PMD82: 3-D Printing is Revolutionizing the Medical Devices World, But Are Payers Ready?

Nuryyeva E, De Wilde R

Upcoming Presentations

ATS International Conference

May 13-18, 2016; San Francisco, CA, USA

POSTERS

Gender Differences by Age in St. George's Respiratory Questionnaire Total Scores and Self-reported Overall Health among Subjects with and without COPD in the COPDGene Cohort

DeMeo DL, Han MK, Regan EA, Yadao A, Kavati A, Vegesna A, Keininger D, **Wilcox TK, Ramagopalan S, Pereira M**, Make BJ

Gender Differences by Age in Symptoms, Airflow Limitation, Exacerbation Risk and GOLD Combined Assessment among Subjects with COPD in COPDGene Cohort

DeMeo DL, Han MK, Regan EA, Yadao A, Kavati A, Vegesna A, Keininger D, **Wilcox TK, Ramagopalan S, Pereira M**, Make BJ

Respiratory Symptom Patterns Over One Year in Patients with COPD: Results from the Acute Exacerbation and Respiratory Infections (AERIS) Study

Sung R, Allinder M, Aris E, Bourne S, Devaster J, Kim V, **Leidy NK,** Locantor N, Mannino F, Ostridge K, Peeters M, Tal-Singer R, Welch L, Weynants V, Williams N, Miller B, Wilkinson T

How `Stable' is Stable COPD? Daily Symptom Variability Of Subjects Enrolled in the SPIROMICS Exacerbation Sub-Study

Ancy KM, Oromendia CI, Ballman KV, **Leidy NK, Malley KG,** Anderson WH, Barr RG, Bleeker E, Bowler RP, Carretta EE, Cooper CB, Couper DJ, Doerschuk CM, Dransfield MT, Hansel NN, Hoffman EA, Kanner R, O'Neal WK, Paine R, Peters SP, Scholand MB, Woodruff PG, Han MK, Martinez FJ

AHS 58th Annual Scientific Meeting

Jun. 9-12, 2016; San Diego, CA, USA

POSTERS

Methods for Addressing Challenges for Evaluating Patient Reported Outcomes in Clinical Trials of Prophylactic Treatments for Migraines

Roberts L, Oko-Osi H, Hareendran A, Mannix S, Corey-Lisle P, Desai P, Sapra S

Reflecting Patients' Perspectives in Measuring Migraine-related Impacts on Functioning: A Qualitative Study with Migraine Patients

Skalicky A, Mannix S, Hareendran A, Corey-Lisle P, Widnell K, Buse DC, Desai P, Sapra S

AAIC - 2016

July 24-28, 2016; Toronto, Canada

Oral Presentation

Simulation Study on Early Treatment with a Hypothetical Disease Modifying Therapy (DMT) on Time in Institutional Care for Patients with Alzheimer's Disease (AD)

Tafazzoli A, Dos Santos R, Krotneva M, Ishak J, Kansal A

32nd ICPE

Aug. 25-28, 2016; Dublin, Ireland

SYMPOSIUM

Who To Ask and How? Preference-Based Methods for Benefit-Risk Assessment

Marsh K, Hillege HL, Ataher Q, **Tervonen T**

PRE-CONFERENCE COURSE

Selection of Databases for Pharmacoepidemiology Research

Reynolds M

WORKSHOP

What's in a Code? Algorithm Validation in Drug Safety Studies

Nordstrom BL, Weiss S, Lanes S, Wang C

ORAL PRESENTATION

Development and Validation of an Algorithm for Identifying Pediatric Patients with Type 2 Diabetes in Claims Data

Teltsch D, Swain RS, Farsani SF, Brodovicz KG, Kaspers S, **Huse S**, Sicignano N, Cristaldi C, **Nordstrom BL**, Bartels DB

POSTERS

An Analysis of Characteristics of Post-Authorization Safety Studies Registered on ENCePP

Ramagopalan SV, Wasiak R, Lambrelli D

Difference in the Rate of Multiple Sclerosis-Related Hospitalizations in Portugal between 2008 and 2013

Pereira M, Lambrelli D, Wasiak R, Ramagopalan SV

Prevalence of Bone Metastases in Patients with Prostate Cancer: A Meta-Analysis

Fahrbach K, Amelio J, **Xu Y**, **Abogunrin S**, Talbot S, Booth E, Niepel D, Body JJ

Risk Factors for Major Bleeding Events in Rivaroxaban Users with Atrial Fibrillation: A Nested Case-Control Study

Simeone JC, Tamayo SG, **Nordstrom BL**, Patel MR, Yuan Z, Sicignano NM, Peacock WF

Social Media Mining to Investigate Multiple Sclerosis Treatment Patterns and Adverse Effects.

Cooper S, Wasiak R, Ramagopalan SV

ISPOR 7TH Asia-Pacific Conference

Sep. 3-6, 2016; Singapore

SHORT COURSE

Budget Impact and Cost Analysis

Caro JJ, Lai A

ISOQOL 23RD Annual Conference

Oct. 19-22, 2016; Copenhagen, Denmark

WORKSHOPS

An Introduction to Health-Related Quality of Life Assessment

Gelhorn H, Wyrwich K

Clinical Outcomes Assessment in a Multi-Cultural Context: Measurement Challenges and Solutions - A Collaborative Workshop by the Psychometric and Translation & Cultural Adaptation Special Interest Groups

Hudgens S, Regnault A, McLoud L, Martin M, **Eremenco S**

Concept Elicitation for the Development of Clinical Outcome Assessments (COAs) – Qualitative Methodological Approaches for Data Collection, Analyses and Reporting

Skalicky A, Hareendran A, Magasi S

Recent Presentations

HTAi 2016 Annual Meeting

May 10-14, 2016; Tokyo, Japan

ISSUE PANEL

Patient Centered Decision Making: How Multi-Criteria Decision Analysis Can Help Capture the Patient Voice

Caro JJ, Hamed A, Wibulpolprasert S, **Marsh K**, Youngkong S

26TH Congresso Nazionale SID

May 4-7, 2016; Rimini, Italy

POSTER

Age-Related Differences in Patients' Preferences for Profiles of Glucagon-like Peptide-1 Receptor Agonist (GLP-1RA) Diabetes Treatments in the United Kingdom: A Discrete Choice Experiment

Adetunji O, **Poon JL,** Davies EW, Paczkowski R, Curtis SE, Gentilella R, Boye KS, **Gelhorn HL**

AMCP Annual Meeting

Apr. 19-22, 2016; San Francisco, CA, USA

POSTER

Real-world Effectiveness of Anti-TNF Switching in Psoriatic Arthritis: A Systematic Review of the Literature

Reddy SM, **Crean S, Martin AL, Burns MD**, Palmer JB

The International Liver Congress 2016

Apr. 13-17, 2016; Barcelona, Spain

Poster

A Systematic Literature Review of the Epidemiology and Economic Burden Associated with Non-Alcoholic Steatohepatitis (NASH)

Sanyal A, **Martin AL**, Cadarette SM, **Burns MD**, Guranlioglu D, Kartman B, Henriksson K, Hansen MB

2016 CADTH Symposium

Apr. 10-12, 2016; Ottawa, ON, Canada

ORAL PRESENTATION

DICE Simulation for HTA: A New, Unifying Method

Caro JJ

6TH Annual Advanced Therapies Summit

Apr. 6, 2016; Stockholm, Sweden

ISSUE PANEL

ATMP Product Reimbursement

Arickx F, Durdy M, **Faulkner E**, Orphanidis A, Osipenko L

ACC 65th Annual Scientific Session

Apr. 2-4, 2016; Chicago, IL, USA

Poster

Comparison of Health and Economic Outcomes of New Oral Anticoagulants for the Prevention of Stroke and Systemic Embolism in Atrial Fibrillation

Zheng Y, **Sorensen SV,** Menown IBA, Gonschior AK, Kleine E, Heinrigh-Nols J, Chouse R, **Kansal AR**

AdvaMed Innovation Summit

Mar. 30-31, 2016; Washington, DC, USA

ISSUE PANEL

How Novel Diagnostics are Changing the Health Care Value Proposition

Faulkner E, Lerner PJ, Hughes D, Denham D

11TH Congress of ECCO - Inflammatory Bowel Diseases

Mar. 16-19, 2016
Amsterdam, Netherlands

POSTERS

A Real-world Study of Outcomes in Biologic-naive Patients with Crohn's Disease and Ulcerative Colitis Initiating Vedolizumab

Raluy-Callado M, Alam N, Donaldson R, Smyth MDL, Khalid JM

Hospitalisations and Characteristics of Patients with Crohn's Disease and Ulcerative Colitis Treated with Vedolizumab in Real-world Clinical Practice: Results from a Multi-centre Study

Reynolds M, Alam N, Raluy-Callado M, Gardstein B, O'Hara D, Smyth MDL, Khalid JM

Real-world Treatment Persistence with Vedolizumab in Patients with Crohn's Disease and Ulcerative Colitis

Raluy-Callado M, Fraeman K, Donaldson R, Reynolds M, Smyth MDL, Demuth D, Khalid JM

8TH Biosimilars Congregation

Mar. 8-9, 2016; London, UK

ORAL PRESENTATION

The Role Payers Can Play in Driving Biosimilar Uptake

Walsh K

Diabetes UK Professional Conference

Mar. 2-4, 2016; Glasgow, Scotland

POSTER

Age-related Differences in Patients' Preferences for Profiles of Glucagon-like Peptide-1 Receptor Agonist (GLP-1RA) Diabetes Treatments in the United Kingdom: a Discrete Choice Experiment

Adetunji O, **Poon JL,** Davies EW, Paczkowski R, Curtis SE, Gentilella R, Boye KS, **Gelhorn HL**

12TH Annual WORLDSymposium 2016

Feb. 29-March 4, 2016
San Diego, CA, USA

POSTER

New Measure to Assess Severity of MPS II: The Disease Severity Score

Amartino H, Burton B, Giugliani R, Harmatz P, Jones SA, Scarpa M, Solano M, Zafeiriou D, **Vernon M, Raluy-Callado M**, Trundell D, **Wiklund I**, Pulles T, Whiteman DAH, Muenzer J

World Pharma Pricing & Market Access Europe

Feb. 23-25, 2016; London, UK

ISSUE PANEL

Value Based Assessment for High Value Products – New Developments and Ascertaining a Fair Sum for New Medicines

Vigier D, Mollon P, **Walsh K**

Next Level's Medical Affairs Leaders Forum Europe (Spring)

Feb. 22-23, 2016; Berlin, Germany

ORAL PRESENTATION

Real World Data Strategy and Programs of Research: A Roadmap for Late Phase Success

Payne K, Lambrelli D

2016 Gastrointestinal Cancers Symposium

Jan. 21-23, 2016; San Francisco, CA, USA

POSTER

Risks of Thromboembolic Events among Patients Diagnosed with Metastatic Pancreatic Ductal Adenocarcinoma Treated with Chemotherapy

Bapat B, **Bhurke S**, Rosen E, **Stokes M, Bhagnani T, Nordstrom B**, Zaknoen S, Qadan A

AIBD 2015

Dec. 10-12, 2015; Orlando, FL, USA

POSTER

Hospitalizations and Characteristics of Patients with Ulcerative Colitis and Crohn's Disease Treated with Vedolizumab in the United States

Reynolds M, Raluy-Callado M, O'Hara D, Alam N, Smyth MDL, Khalid JM

XXI World Congress on Parkinson's Disease and Related Disorders

Dec. 6-9, 2015; Milan, Italy

ORAL PRESENTATION / POSTER

Determination of Minimal Important Difference Thresholds for Parkinson's Disease Questionnaire-39 in Advanced Parkinson's Disease Patients

Antonini A, **Bacci ED**, Sail K, Jalundhwala YJ, Kandukuri PL, Marshall T, Chatamra K, **Wiklund I, Revicki D**

ASH 57TH Annual Meeting and Exposition

Dec. 5-8, 2015; Orlando, FL, USA

POSTERS

A Frailty Scale Predicts Outcomes in Patients with Newly Diagnosed Multiple Myeloma Who Are Ineligible for Transplant Treated with Continuous Lenalidomide Plus Low-Dose Dexamethasone in the FIRST Trial

Facon T, Hulin C, Dimopoulos MA, Belch A, Meuleman N, Mohty M, Chen WM, Kim K, Zamagni E, Rodriguez-Otero P, Renwick W, Rose C, Tempescul A, Palumbo A, **Guo S**, Sturniolo M, Ervin-Haynes A, Fermand JP

Economic Burden of Infections Following Allogeneic Hematopoietic Cell Transplant for Hematologic Malignancies

Berger A, Grubb W, **Huse S**, Mohanty M, Ferraro J, Daniels M, Levin W

AAAP 26TH Annual Meeting and Symposium

Dec. 3-6, 2015
Huntington Beach, CA, USA

POSTER

Psychometric Evaluation of the Short Opiate Withdrawal Scale-Gossop in Patients Undergoing Opioid Detoxification

Vernon MK, Reinders S, **Mannix S**, Gullo K, Gorodetzky CW, Clinch T

BSRM 2015 Annual Meeting - Neuromuscular Conditions - Rehab Issues and Interventions

Dec. 1, 2015; London, UK

POSTER

Resource Utilisation and Costs in Patients with Post-Stroke Spasticity in the United Kingdom

Raluy-Callado M, Cox A, MacLachlan S, Dinet J, Gabriel S

7TH International Pharmacoeconomic Conference on Alzheimer's Disease (IPECAD)

Nov. 19-20, 2015; Boston, MA, USA

ORAL PRESENTATION

An ACE for Alzheimer's Disease: State of the Art Modeling

Caro JJ

AASLD's The Liver Meeting 2015

Nov. 13-17, 2015; San Francisco, CA, USA

POSTERS

Cost-effectiveness of Combination Daclatasvir-Sofosbuvir for Genotype 3 Chronic Hepatitis C Infection in the United States

Saint-Laurent Thibault C, Moorjaney D, Ganz ML, Sill B, Hede S, Yuan Y, Kalsekar A, Gorsh B

Development of a Clinician Reported Outcome Tool for Assessment of Hepatic Encephalopathy

Bajaj J, Bass NM, Frederick RT, **Coyne K**, Margolis MK, Coakley DF, Mokhtarani MM, Jurek M, Scharschmidt BF

Development of an Electronic Diary for Caregivers of Patients with Overt Hepatic Encephalopathy

Frederick RT, Ghabril M, **Coyne K**, Margolis MK, Santoro M, Coakley DF, Mokhtarani M, Scharschmidt BF, Jurek M

Predictors of Treatment Adherence and Discontinuation in Department of Defense (DoD) Health Care Beneficiaries Treated for Chronic Hepatitis C 2004-2013

Teltsch D, Walker DR, **Nordstrom B, Fraeman K**, Kronmann K, St. Clair KJ

AHA Scientific Sessions 2015

Nov. 7-11, 2015; Orlando, FL, USA

POSTER

Cost-Effectiveness of Ivabradine as a Treatment for Systolic Chronic Heart Failure in the United States

Kansal AR, Cowie M, Kielhorn A, **Krotneva S, Tafazzoli A**, Zheng Y, Yurgin N

International Scientific and Practical Conference

Nov. 2, 2015; Moscow, Russia

ISSUE PANEL

Multi-criteria Decision Analysis (MCDA) as a Measure of Innovation

Marsh K

Publications

Askew RL, Cook KF, **Revicki DA**, Cella D, Amtmann D. Evidence from Diverse Clinical Populations Supports Clinical Validity of PROMIS Pain Interference and Pain Behavior. *J Clin Epidemiol.* 2016 Feb 27. pii: S0895-4356(16)00145-1. doi: 10.1016/j.jclinepi.2015.08.035.

Augustovski F, Zarante V, **Caro JJ**, Ferraz MB. Editorial: Brief Latin American Update: One More ViHRI Annual Issue, and Another Exciting Biennial ISPOR Conference. *Value Health Reg Issues.* 2015 Dec; 8:137-138.

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Blume SW, **Yeomans K**, Allen-Ramey F, Smith N, Kim H, Lockey RF, Nichol MB. Administration and Burden of Subcutaneous Immunotherapy for Allergic Rhinitis in U.S. and Canadian Clinical Practice. *J Manag Care Spec Pharm.* 2015 Nov;21(11):982-990.

Bourbeau J, Lavoie K, Sedeno M, De Sousa D, Erzen D, Hamilton A, Maltais F, Troosters T, **Leidy NK**. Behaviour-Change Intervention in a Multicentre, Randomised, Placebo-Controlled COPD Study: Methodological Considerations and Implementation. *BMJ Open.* 2016 Apr 4;6(4):e010109.

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Capkun G, Dahlke F, Lahoz R, **Nordstrom B**, Tilson HH, Cutter G, Bischof D, Moore A, **Simeone J, Fraeman K**, Bancken F, Geissbuhler Y, Wagner M, Cohan S. Mortality and Comorbidities in Patients with Multiple Sclerosis Compared with a Population without Multiple Sclerosis: An Observational Study Using the US Department of Defense Administrative Claims Database. *Mult Scler Relat Disord.* 2015 Nov;4(6):546-554.

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Caro JJ, Moller J, Karnon J, Stahl J, **Ishak J**. Discrete Event Simulation for Health Technology Assessment. *CRC Press, Taylor & Francis Group*; 2015.

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ISPOR Task Force Releases Two New Reports Highlighting Growing Relevance of MCDA

Dr. Kevin Marsh from Evidera Interviewed in *Value & Outcomes Spotlight*

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) has published two new reports focused on Multiple Criteria Decision Analysis (MCDA). The first, titled "Multiple Criteria Decision Analysis for Health Care Decision Making – An Introduction: Report 1 of the ISPOR MCDA Emerging Good Practices Task Force," appeared in ISPOR's January/February 2016 issue of *Value in Health*. The second, titled "Multiple Criteria Decision Analysis for Health Care Decision Making – Emerging Good Practices: Report 2 of the ISPOR MCDA Emerging Good Practices Task Force," appeared in the March/April 2016 issue of *Value in Health*.

Kevin Marsh, PhD, Executive Director and Senior Research Scientist, Modeling and Simulation for Evidera, was also recently interviewed on behalf of the MCDA Task Force for the March/April 2016 issue of ISPOR's *Value & Outcomes Spotlight.* This interview can be access on ISPOR's website at www.ispor.org/ValueOutcomesSpotlight.

MCDA is increasingly used to support healthcare decision making, including molecule investment decisions, patient-centered benefit risk assessment, health technology assessment, and prescription decisions. The diversity of MCDA methods, however, can be an obstacle to researchers. The Task Force was established to help define MCDA and provide good practice recommendations for its use in healthcare. The Task Force outputs will help advance the use of MCDA in healthcare by providing a sound basis for researchers and policy makers to determine which MCDA approach is appropriate for their needs, and then support them to implement the chosen approach.

More information on the ISPOR Task Force, including both reports, can be found at www.ispor.org/Multi-Criteria-Decision-Analysis-guideline.asp. *For more information on Evidera's capabilities in MCDA, visit www.evidera.com/MCDA.*

FDA Releases Draft Guidance on use of the "E-RS:COPD" to Measure Respiratory Symptoms in Stable COPD

In March 2016, the Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration (FDA), released its second draft qualification guidance document for a patient-reported outcome (PRO) measure: Evaluating Respiratory Symptoms in Chronic Obstructive Pulmonary Disease, a Patient-Reported Outcome, for the Measurement of Severity of Respiratory Symptoms in Stable Chronic Obstructive Pulmonary Disease: Qualification for Exploratory Use.

The Evaluating Respiratory Symptoms of COPD (E-RS™:COPD) was developed by Evidera as part of the EXACT-PRO Initiative, a multi-year, multi-sponsor project initiated and led by Evidera. The E-RS is a derivative of the EXACT®, the first PRO measure qualified by the FDA (January 2014), and used to assess acute exacerbations of COPD. The E-RS:COPD was designed to measure respiratory symptoms in patients with stable COPD and test the effects of treatment on this outcome. The instrument has been and is being used in multiple clinical trials and academic studies. Evidera maintains copyrights to the EXACT and E-RS and facilitates its use in clinical research.

"Respiratory symptoms can be disabling to patients with COPD, and symptomatic relief is an important goal of treatment. The E-RS:COPD will help us improve our understanding of the effects of treatment on these important symptoms," said Nancy Kline Leidy, PhD, Senior Vice President, Scientific Affairs for Evidera and Principal Investigator and Director of the EXACT-PRO Initiative. "We're pleased the FDA has recognized both the EXACT and E-RS as outcome measures for use in drug development trials of COPD through the qualification process."

More than 12 million people in the U.S. have been diagnosed with COPD, and an additional 12 million in the U.S. are thought to have undiagnosed COPD according to the National Institutes of Health. COPD is the third leading cause of death in the U.S. (Centers for Disease Control and Prevention). There is no cure, but every effort is being made to understand, treat, and manage the effects of this disabling disease.

To learn more about the E-RS and EXACT, visit exactproinitiative.com.

Evalytica Recognized Among Top 10 Analytics Solution Providers in 2016

Evalytica®, a cloud-based, software platform by Evidera, was included in *Pharma Tech Outlook's* Top 10 Analytics Solution Providers 2016 list announced in January 2016, for its expertise in redefining the intersection of technology and healthcare analytics with its innovative next generation software for real-world evidence development. The positioning is based on evaluation of Evalytica's capabilities in providing innovative, real-world analytic technologies.

Pharma Tech Outlook is an online, monthly magazine that covers the most important and latest developments in the pharmaceutical industry. The annual list of companies is selected by a panel of experts and members of Pharma Tech Outlook's editorial board to recognize and promote technology entrepreneurship. Evalytica has been selected after being evaluated across a dozen quantitative and qualitative elements. Experts at Pharma Tech Outlook took into consideration Evalytica's experience, industry recognition, technical certifications, market presence, and positive client reviews. Although Evalytica just launched in 2015, the life sciences industry has expressed significant interest in subscribing to the product.

To learn more about Evalytica, visit: www.evalytica.com.

Dr. Jaime Caro Wins ISPOR's 2016 Marilyn Dix Smith Leadership Award

Evidera is pleased to announce that Dr. Jaime Caro, Chief Scientist, is the recipient of ISPOR's 2016 Marilyn Dix Smith Leadership Award. Marilyn Dix Smith was the Founding Executive Director of ISPOR, conceiving and building the society focused on pharmacoeconomics and outcomes research. Marilyn's vision was to create an organization that identifies, supports, and provides leadership in the field. This award was created to acknowledge one individual each year who has demonstrated a career of extraordinary leadership to ISPOR and the field.

Dr. Caro has played a leadership role in the field for more than 20 years. He has shaped policy in many countries around the world, developed and instructed courses at various universities, held multiple ISPOR leadership positions, and has been instrumental in helping increase the prominence, relevance, and impact of the field.

ISPOR will present Dr. Caro this award at its annual meeting in Washington, DC, May 21-25, 2016.

Evidera Advances the Use of DICE: A Health Economic Modeling Approach Designed to Meet HTA Requirements

Evidera recently announced new modeling capabilities using Discretely Integrated Condition Event (DICE) simulation, the first modeling technique specifically designed to meet decision-analytic modeling needs for health technology assessment (HTA). It is a flexible and transparent technique that allows for execution of a wide range of studies, including traditional health economic analyses such as budget impact, cost-consequence, cost-effectiveness, and cost-utility.

"It has been very gratifying to see how well this method has been received," said Dr. Jaime Caro, Chief Scientist at Evidera. "Within a few minutes of viewing a short presentation, everyone 'gets it' and sees the tremendous potential of DICE. As a result, many companies are adopting it for their disease models and health economic submissions."

Dr. Caro introduced the DICE simulation method in a recent publication, *Discretely Integrated Condition Event (DICE) Simulation for Health Technology Assessment* (available at http://www.ncbi.nlm.nih.gov/pubmed/26961779.) Evidera has created a proprietary platform for implementing DICE in Microsoft Excel®, called EviDICE™. "EviDICE provides an efficient way to consistently implement modeling studies," said Dr. Caro. "Our aim is to reduce the burden of programming and verification while minimizing the opportunity for errors that impair trust in modeled outcomes."

This announcement arrives on the heels of the release of Evidera's innovative Alzheimer's disease (AD) ACE simulator, implemented using DICE. AD ACE is designed to address the complex interactions between multiple components of AD pathology (e.g., biomarkers, cognition, behavior, function) and their roles in disease progression. It is being used across a range of modeling analyses and is applicable to studies ranging from early what-if assessments to formal HTA submissions.

To learn more about DICE, see the article in this issue of *The Evidence Forum* or visit http://www.evidera.com/dice/. To learn more about AD ACE, visit http://www.evidera.com/ace/.

Upcoming Webinars

June 15, 2016, 10:00am ET

Which Method to Use for Capturing Patient Preferences in Benefit-Risk Assessment

June 28, 2016, 10:00am ET

How are Patient Preferences Used? Examples from Industry

COPD Foundation and Evidera Receive "Best Personalized Medicine Advance or Application" Award

Evidera and the COPD Foundation were awarded "Best Personalized Medicine Advance or Application" at Informa's 2016 Clinical & Research Excellence (CARE) Awards, held on April 27 in Boston, MA.

Evidera and the Foundation's COPD Biomarker Qualification Consortium (CBQC) were recognized for their work leading to the FDA's qualification of plasma fibrinogen as a biomarker for clinical trials of COPD. This is the first biomarker for COPD and the seventh biomarker qualified by the FDA to date. The award recognizes the contributions of this dedicated team to advancing the promising field of personalized medicine. The judges commented that this project exemplified a successful public-private collaboration.

The CARE Awards were established to honor those who work in clinical research and development to make human lives better with new medicines. Jason Simeone, PhD, Research Scientist for Evidera and Debbie Merrill, Senior Director of CBQC were in attendance to accept the award.

"We enjoyed partnering with the CBQC on this project," said Nancy Kline Leidy, PhD, Senior Vice President of Scientific Affairs for Evidera. "Jason and the Evidera analytics team were active in every step of the process, from design and implementation to interpretation and qualification. This CARE award recognizes the work the Evidera-CBQC partnership has accomplished to date, driven by a commitment to improving the efficiency and effectiveness of pharmaceutical trials in COPD. We look forward to continuing our work together."

A complete listing of all CARE award winners can be found on Informa's website (https://ibiawards.com/careawards).

For more information on the COPD Foundation, visit www.copdfoundation.org. If you are interested in learning more about this project or Evidera's capabilities, contact us at info@evidera.com.

Evidera Welcomes New Senior Staff

Grammati Sarri, DiDS, MSc, PhD, is a Research Scientist for Evidera's Meta Research group in London, UK. Dr. Sarri has over 10 years of experience as a university teacher, clinical and epidemiological researcher, systematic reviewer, and statistical advisor in academic, advisory body, and health policy settings. She spent over six years as a senior research fellow involved in producing evidence synthesis (quantitative and qualitative reviews and complex meta-analyses including network meta-analyses [NMAs]) to inform the National Institute for Health and Care Excellence (NICE) guidelines in a wide range of health conditions. Latterly, Dr. Sarri became a NICE Clinical Guideline Lead and had overall scientific and operational responsibility for guideline development from scoping to publication, including provision of expert opinion and quality assuring methodological aspects across different guideline topics. The role included being the lead author of two NICE guidelines: *Menopause: Diagnosis and Management* and *Preterm Labour and Birth* (both published in November 2015).

Dr. Sarri's methodological expertise is based on epidemiological and statistical knowledge and experience gained through formal academic qualifications and professional participation in working methodological groups. Her publication portfolio spans various clinical and methodological areas, such as articles reporting systematic reviews conducted to inform NICE guidelines, official summaries of NICE guidelines published in the BMJ and presentations of statistical analyses from multiple epidemiological and clinical studies. Dr. Sarri has also been invited to provide expertise on decision-making at several international meetings, and she was the expert advisor to the World Health Organization in the use of NMA in developing its *Guidelines for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B Infection.*

Dr. Sarri qualified as a clinical dentist at the University of Athens (Greece) and has an MSc in Dental Public Health from the Institute of Dentistry, Barts and The London School of Medicine and Dentistry, and a PhD in Oral Epidemiology from the University of London.

Vernon F. Schabert, PhD, joined Evidera as a Senior Research Scientist in Real-World Evidence. Dr. Schabert is an internationally-recognized health outcomes researcher with 20 years of experience in health services research, developing evidence-based insights for health technology manufacturers, healthcare providers, payers, and regulatory agencies. His interdisciplinary approach to healthcare issues blends creative techniques from psychology, economics, systems analysis, and human factors research. He is an expert at evaluating the quality of data in healthcare business systems, then improving the value that those data provide to healthcare stakeholders.

Dr. Schabert's areas of expertise include the measurement of medication adherence, dosing, and treatment sequencing; use of biologic therapies; case mix adjustment; inpatient safety; and clinical and functional outcomes in post-acute care. His work has been published in such peer-reviewed journals as *Melanoma Research, International Journal of Rheumatic Disease, American Journal of Otolaryngology, American Journal of Managed Care, Journal of Managed Care Pharmacy, Current Medical Research & Opinion,* and *Journal of Medical Economics*. He has conducted analyses of electronic healthcare data from 14 countries across North America, Europe, and Asia. He has also collected and analyzed real-world evidence from prospective trials, patient-reported outcomes instruments, and patient surveys.

Prior to joining Evidera, Dr. Schabert held positions at LASER Analytica, IMS Health, and Thomson Medstat (now Truven Healthcare Analytics). At IMS Health, he led the company's global center of excellence in database analysis. Dr. Schabert holds a PhD in Social and Personality Psychology from Stanford University, and an A.B. in Psychology from Princeton University.

Ken Walsh, MA, MSc, is a Senior Principal in Global Payer Strategy for Evidera. Mr. Walsh has over 10 years of extensive pricing strategic management and regulatory consulting experience with top global pharmaceutical firms in the UK, U.S. and across Asia, and is now responsible for managing Evidera's Payer Strategy group in London. Mr. Walsh brings comprehensive knowledge of integrated issues regarding the evolving global healthcare environment, including market access, pricing and reimbursement, public policy, and product commercialization in the U.S., Europe, and emerging markets. His specialties include qualitative and quantitative pharmaceutical global pricing and market access strategy development.

Prior to joining Evidera, Mr. Walsh was Head of Pricing for Emerging Markets at GlaxoSmithKline where he managed approximately 140 markets with a broad portfolio of therapeutic areas and directed all strategic pricing initiatives for the Latam, Africa, MENA-CIS, Asia and Australasia regions. He has also worked at Sandoz (a Novartis Company) where he led global pricing and market access for the Biosimilars and Oncology business unit, and prior to that held strategic consulting positions in the U.S. and Singapore, including roles at Cambridge Pharma, GfK, Kantar Health and Bridgehead.

Ken received his MA (hons) in Economics from Heriot-Watt University and also holds an MSc in Finance from Cass Business School.

Karen Yeomans, BSc, is a Senior Manager in the Real-World Evidence group at Evidera in Montreal, Quebec. Prior to joining Evidera, Ms. Yeomans worked in product research and development (PR&D) at Merck Frosst. She has nearly 10 years of experience in the consulting industry and has led a variety of sponsored studies in real-world evidence generation, including retrospective chart reviews, time-and-motion studies, patient and physician surveys,

and longitudinal studies. Her work has spanned the fields of chronic pain, constipation, allergy, oncology, migraine, smoking cessation, acne, and rosacea, and has resulted in nine peer-reviewed articles and 25 conference presentations. Ms. Yeomans completed her BSc at McGill University with an emphasis in Biochemistry. She is fluent in English, French, and Spanish.

Meet Evidera's Real-World Evidence Experts

Evidera has one of the largest and most diverse teams of experts in the industry. Our experts in real-world evidence are listed here, and a complete listing of all Evidera experts can be found at http://www.evidera.com/why-evidera/our-experts/.

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Real-World Evidence and Meta Research

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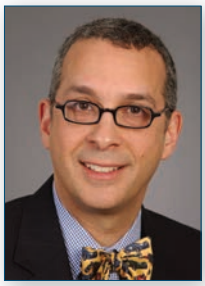

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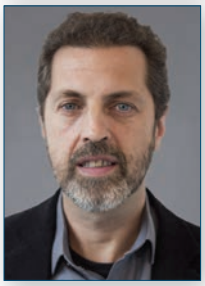

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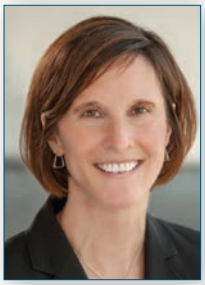

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