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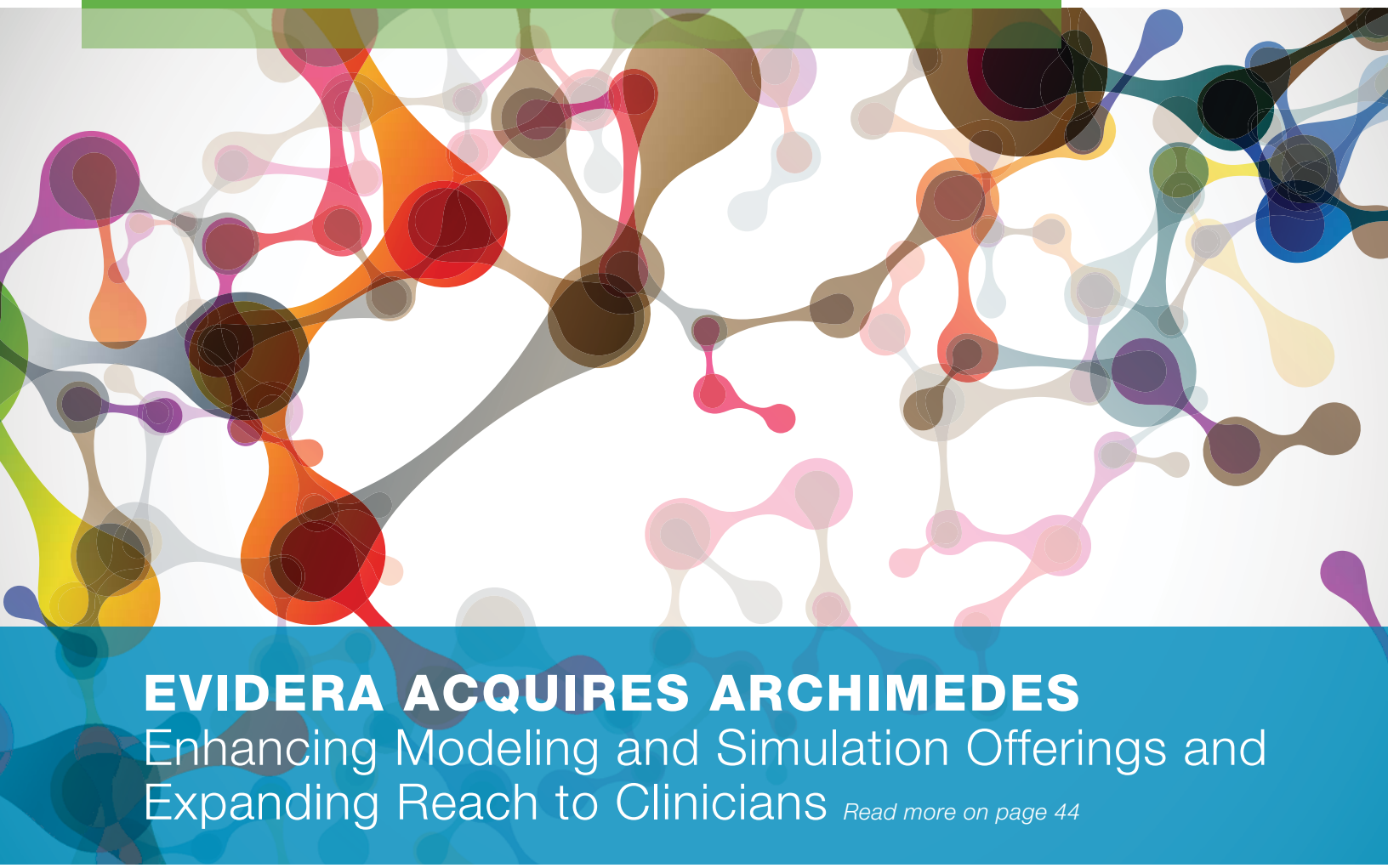

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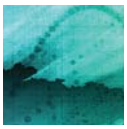


Rare Disease Treatments—Evidence, Value, Insights

Thomas Rising, DPhil, Managing Consultant, Global Payer Research and Strategy;
Alex Ward, PhD, MRPharmS, Senior Research Scientist, Health Economics and Epidemiology;
Karen Sandman, PhD, U.S. Practice Lead, Global Market Access Communications

OVERVIEW OF RARE DISEASES AND ORPHAN DRUGS

Rare, or "orphan", diseases are those diseases which affect a small percentage of the population, and as a result, have traditionally received less attention in the development of treatments. In the last 30 years, there has been a larger focus on addressing the treatment needs of these diseases. In 1983, orphan drug status was introduced in the U.S. through the Orphan Drug Act,[1] to help incentivize drug manufacturers to develop treatments for very serious rare diseases where, without these incentives, it was considered unlikely that manufacturers would generate a return on the investment and, therefore, not investigate and develop treatments for these rare conditions. The European Medicines Agency (EMA) later established the Orphan Medicinal Product Designation[2] in the European Union, with Japan and other countries following. Orphan drug policies are different in each country and key criteria and benefits are summarized for the U.S., EU and Japan in *Table 1.*

The number of current orphan drug designations has doubled in the past seven years, indicating success in the orphan drug policies. While incentives vary between member states within the EU, one key benefit for all countries in *Table 1* is market exclusivity for a specified number of years. While orphan drug status can mean a lower burden of proof, high willingness to pay, and easier funding compared with non-orphan drugs in some countries (specifically in the EU), this status does not necessarily allow for faster market access, and there are only a few markets where there are different pricing and reimbursement processes for orphan drugs compared with non-orphan drugs. For example, in Germany drugs are now required to undergo a cost-benefit analysis, however, orphan drugs can bypass that requirement if they have a turnover of <50 million Euros/year

(although the Gemeinsamer Bundesausschuss or Joint Federal Committee [GBA] is considering removing this incentive). In the UK, as of late March 2013, orphan drugs are evaluated by the National Institute for Health and Clinical Excellence (NICE), which has cost effectiveness requirements for drug approval, causing concern with patient advocacy groups that this may lead to future orphan drugs being more easily rejected.

ORPHAN DRUG COSTS

In looking at the cost of orphan drugs, there is clear correlation between disease prevalence and cost/patient *(see Table 2)*, which stands to reason if one considers that a disease such as Fabry disease has treatment costs at approximately £100,000/year/patient with a prevalence of 1-5/10,000, while N-acetylglutamate synthetase deficiency treatment costs up to $2 million dollars with a prevalence of only 0.01/10,000. Fewer patients equates to a higher cost/treatment/patient to recoup development costs. With nearly 4,000 orphan drug designations in the EU and U.S., over 500 with market authorization and thousands of potential rare diseases needing new treatments, there will be a considerable impact to payer budgets in the near future. Fifteen years ago, orphan drug sales were approximately 5% of the worldwide prescription drug markets, and today that has risen to 14% with an increase to 16% anticipated in five years. Payers are therefore pushing strongly against the high-cost orphan drugs, unless there is significant demonstrable benefit to patients.

EVIDENCE-BASED VALUE PROPOSITIONS FOR ORPHAN DRUGS

Orphan drug status does have its advantages but does not guarantee positive reimbursement or a favorable view on the therapeutic value of an orphan product, so the development of an evidence-based value story is paramount to addressing the many market access challenges associated with orphan drugs, particularly in pricing and reimbursement negotiations and other stakeholder communications.

KEY CRITERIA AND BENEFITS FOR ORPHAN DRUG POLICIES IN KEY COUNTRIES

				
Criteria	Regulation Since	1983	2000	1993
	Prevalence	< 200,000	< 5 / 10,000	< 50,000
	Designated / MA	2907 / 447*	965 / 67*	293 / 179**
Benefits/Incentives	Protocol Assistance	Yes	Yes	Yes
	Grants & Lower Fee	Yes	Yes	Yes
	Tax Credits	Yes	By MS	Yes
	Market Exclusivity	7 Years	10 Years	10 Years

**As listed on FDA/EMA websites (26 September 2013) **As listed on MHLW website (12 November 2013)*

table 1

TERMINOLOGY: ULTRA-ORPHAN

Orphan drugs for oncology indications are seen as a distinct class for market access since oncology is a major subgroup within orphan diseases, with only four main oncology areas not receiving orphan drug designation. As a result, we are focusing primarily on non-oncology orphan diseases in this article. It is also worth highlighting here that payers across all markets are seeing a huge growth in the number of expensive orphan drugs, and as a result, orphan drugs across different indications are being viewed as more of a distinct collection or group having a significant budget impact. That has prompted some markets to further define very rare diseases within the orphan group as ultra-orphan *(see Figure 1)*. This has led to a payer perception that the ultra-orphan is now the 'new' orphan since there are so many orphan drugs in the marketplace.

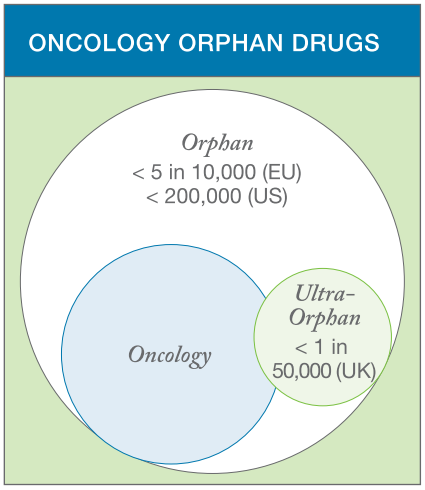
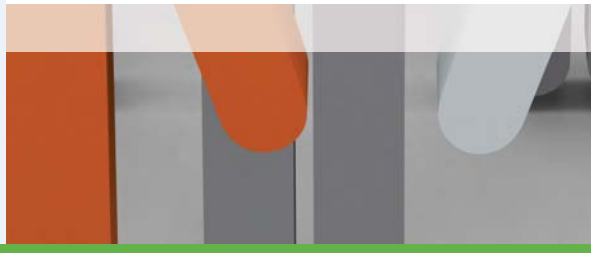


figure 1



COST OF ORPHAN DRUGS				
Drug	*Indication*	*Disease prevalence (per 10,000)***	*Approximate annual cost per patient**	*Date of marketing authorization*
Agalsidase alfa	Fabry disease	1 to 5	£110,000	May 4 2001 EU
Ivacaftor	Cystic fibrosis (G551D mutation)	1 to 5 (4% to 5% have G551D mutation)	$360,000 £182,625	Dec 20 2006 US May 24 2012 EU
Imiglucerase	Gaucher disease type I	0.1 to 0.9	$520,000 £290,000	May 23 1994 US Nov 17 1997 EU
Eculizumab	Paroxysmal nocturnal haemoglobinuria	0.01 to 0.09	$545,000 £250,000	Mar 19 2007 US Oct 17 2003 EU
Idursulfase	Mucopolysaccharidosis II	0.01 to 0.09	$675,000 £410,000	Jul 24 2006 US Jan 8 2007 EU
Alglucosidase alfa	Pompe disease	0.1 to 0.9	$850,000 £260,000	Apr 28 2006 US Mar 29 2006 EU
Carglumic acid	N-acetylglutamate synthetase deficiency	<0.01	$2,140,000 £745,000	Jan 20 1998 US Oct 18 2000 EU

**UK price calculations based on unit costs obtained from British National Formulary 2012, U.S. prices from average wholesale price in the Red Book 2012. All calculations based on prescribing information in a patient of 70kg except idursulfase, which is based on a patient of 48kg.*
***Orphanet. Rare disease prevalence. 2012; http://www.orpha.net/consor4.01/www/cgi-bin/Disease.php. Accessed October 2012.*

table 2

When starting to develop value stories, it is imperative to address questions from the payer perspective.

1. Burden of illness/unmet need
   a. Why does the disease need to be treated? How bad is it? Why aren't the existing treatments good enough?
   b. If there are no existing options (e.g., for some ultra-orphan diseases), is supportive care good enough or is a disease-modifying treatment really needed?

2. Clinical value
   a. What makes the product unique (e.g., dosing, mechanism of action, safety)?
   b. Does the product work?
   c. How well does the product work?
   d. What is the efficacy from the randomized controlled trials?
   e. How does it compare to other options, including competitor treatments?

3. Economic/outcomes value
   a. Is the product worth the money? (addressing cost-effectiveness)
   b. What is the budget impact of the treatment? Is it affordable? (often a more useful argument than cost-effectiveness since the overall budget impact tends to be minimal to modest given the rarity of the disease)
   c. What is the value to patients, caregivers and families? Does the product offer meaningful benefits in terms of quality of life and other patient perspective issues?

CHALLENGES AND STRATEGIES IN DEVELOPING AN EVIDENCE-BASED VALUE STORY

Burden of illness/unmet need

Since orphan diseases are, by definition, rare, there is usually less research and literature to establish the burden of illness. So although healthcare decision makers may have true empathy for patients and caregivers, they often do not have much awareness about the clinical, humanistic, and economic burden of a particular disease. Unfortunately, this can result in extreme or unrealistic restrictions on patient access to life-changing therapies.

Likewise, when a population is so small, sometimes the unmet need goes unnoticed. Patients often undergo invasive, inconvenient, and often ineffective therapies that would not even be considered acceptable for larger populations. Additionally, patients often have to travel long distances to get access to care at specialist centers, which can severely impact quality of life issues, such as jobs, school attendance, etc. Lastly, because these diseases can be very severe, patients may not reach appropriate therapeutic goals with the existing standards of care, but they

often accept sub-optimal outcomes as "the best they can hope for". With scientific innovation bringing forth products that can be life-changing, it becomes important to emphasize that mediocre quality of life is not acceptable for patients simply because they have a rare disease.

When addressing these issues with payers, it can be helpful to provide expanded disease background information, including solid evidence of the burden on patients and caregivers. Emphasizing sub-optimal outcomes that exist with the current standard of care is also helpful, and this can be done using registration trials for the new product that show baseline data on the patients without any disease-modifying treatment. Collecting real-world data to show patient and caregiver burden can be challenging, however, due to the low population with the disease which makes identifying patients and caregivers difficult in some cases.

While baseline data on patients enrolled in a clinical trial sometimes can be a relevant source of evidence about the health status of patients receiving standard care, additional data are usually collected to address the data gaps. Patient and/or caregiver surveys can help demonstrate the true burden of an under-recognized illness and unmet need. The studies are typically conducted by working in close collaboration with patient advocacy groups, centers of excellence or existing registries. However, it is also increasingly common to explore the feasibility of identifying patients in extremely large databases of medical claims or electronic medical records and also linking these with patient surveys and chart reviews. As few of the orphan diseases have specific codes, a sophisticated approach is essential to use these databases, which typically includes investing in development of coding algorithms to identify the relevant cases and confirming these are capturing data collected from the intended patient population. The appropriate approaches vary widely among different treatments and diseases.

Clinical efficacy and comparative effectiveness

Demonstrating clinical efficacy and comparative effectiveness is essential for any type of drug, whether the disease is rare or not, but there are some particular challenges associated with rare diseases. Although there is some leniency on the part of healthcare decision makers when it comes to orphan diseases, there can be situations where healthcare decision makers challenge the trial design for orphan drugs. Trials are typically very small due to the patient population being very small, and the pivotal trials for a drug may use surrogate endpoints, particularly if it is a chronic disease. Since there is not always time to wait for long-term clinical endpoints to occur, biomarkers or other types of short-term endpoints may be used, so the combination of a small trial and potentially only surrogate endpoints can lead to questions and challenges about the trial design.

Another issue is that some payers have a strong preference for comparative effectiveness, head-to-head trials, which may not be available if a drug is the only available disease-modifying treatment. If the disease is particularly serious, it may be unethical to conduct a placebo-controlled trial, so sometimes the Phase 3 trials for an orphan drug may actually be single arm, which can lead to questions about the comparative efficacy versus standard of care. Indirect treatment comparisons can be used to identify the comparative effectiveness, but that also can be a challenge to find the right trials to undertake that type of analysis because there may be very few prospectively designed trials in an orphan indication.

PAYERS ARE BECOMING MORE AWARE OF THE OVERALL IMPACT OF ORPHAN DRUGS ON THEIR BUDGETS.

"Nobody understands how companies come to such high prices for orphan drugs… **if the manufacturer thinks this product could be this price (€300K), then this is crazy!** If you can demonstrate life extended by 10 years, then maybe." –France

"€50K is the maximum they can hope for… **the health system cannot afford these kind of prices anymore.**" –Italy

"Just thinking from the economic standpoint—and the fact that the **G-BA are required to save €2 billion in the next year**—the major restriction for this drug may be its cost. If it's too expensive then it would be used later in therapy algorithm." –Germany

"€300K per year is very, very expensive. Depends on the number of patients per region in terms of what kinds of restrictions will be placed. **The restrictions would be heavy, but patients would probably receive the treatment.**" –Spain

Payer leniency for these challenges varies from country to country, but the key is to be very upfront about the appropriateness of the trial or trials that have been conducted for the orphan drug. Confidence that the trial was conducted in the most appropriate, ethical, and clinically sound way is critical, while keeping the message focused on the product's key efficacy benefits in this disease that has substantial burden and unmet needs.

Economic and outcomes value

As mentioned previously, patients and their families and caregivers can experience quite a significant impact on quality of life as a result of having an orphan disease. They spend a lot of time being patients and suffering the consequences of a disease that has often very little visibility and awareness. Particularly in diseases that have this kind of substantial humanistic burden, such as genetic diseases that start in infancy and are chronic and often result in a very shortened life span, quality of life and patient-reported outcome (PRO) data can very much bolster that core efficacy message.

Having surrogate endpoints showing that a biomarker is improved, and to then have immediate evidence showing patients and/or families reporting better outcomes and quality of life, can help to support the core efficacy message. A potential pitfall, however, is that often it seems easier to use the generic quality of life or PRO scales or ones created for a similar disease, but that does not always capture the true impact of a new product for a very specific orphan disease. Therefore, validating a PRO scale or a quality of life questionnaire specifically for the disease that is being studied can be helpful. It is also important to note that quality of life/PRO data are generally seen as a secondary consideration by payers with efficacy and safety being the key product attributes. There may actually be a requirement for quality of life data for rare diseases, but specifying use of disease-specific measurement tools (or at least the data is considered more relevant when disease-specific tools are used). These tools should address any unusual circumstances that patients face with the particular disease, such as travelling long distances for treatment because that is the only treatment option available or measuring psychosocial concerns arising from having a low visibility condition. The recommendation is that these measurements are tested and discussed with payers before developing and finalizing the final PRO and quality of life (QOL) tools.

Perhaps the most hotly discussed aspect of value in orphan drugs is economic value, and this is a challenging issue. As previously established, most orphan drugs are not cheap, and if looking at traditional incremental cost-effectiveness ratio thresholds, most orphan drugs are not seen as cost effective. Different countries are evolving in terms of how they approach economic evaluation for orphan drugs. As noted, budget impact arguments can be more effective than cost-effectiveness analysis simply because, with a rare disease, the overall budget impact is going to be relatively low. Budget impact is also improved by the fact that generally a life-changing, disease-modifying treatment is going to be associated with some cost offsets, such as patients not being hospitalized as often or not having to undergo surgeries and other procedures if their disease is being well controlled on pharmacologic therapy.

In markets that do require cost-effectiveness analysis, there are a few issues to consider in terms of the goals and outputs of economic modeling. So an economic model, even if it does not show that something is cost effective according to traditional thresholds, will be able to provide a framework for capturing health gains and for allowing someone to vary assumptions and then to be able to project the product's clinical value in this burdensome disease.

When planning the evidence to support health technology assessments, a budget impact assessment tool and a cost-effectiveness analysis are always considered. However, there is often a role for epidemiology forecasting, and developing models earlier in the drug development process may be helpful. A few examples illustrating how models can inform evidence generation plans are provided below.

Epidemiology forecasting

- Assess impact of individual characteristics on number of cases eligible for therapy
- Explore impact of diagnostic, genetic, or biomarker tests
- Inform understanding of disease progression, mortality, and established heterogeneity or predictors of outcomes

"Early" models

- Aid decision-making on further studies, prioritize data collection to address gaps
- Use early or proxy data on intervention to understand impact of improving surrogate endpoint(s) on long-term outcomes
- Explore heterogeneity, key outcome drivers, pricing scenarios
- Clinical trial simulation

Economic modeling (CEA/CUA)

- HTA submissions often predict clinical benefits beyond trial period
- Explore economic and health impact
  - Treatment stopping rules to maintain treatment benefit while minimizing cost
  - Subgroups, other scenarios to demonstrate value of therapy

Budget impact assessment

- Forecast budget impact of therapy
- Explore impact of patient access schemes
- Epidemiology inputs key to credible budget impact assessments

A key component of evidence-generation planning includes an assessment of the extent of the data available to populate the models developed to support HTA submissions. Credible inputs are necessary for the model results to impact payer decisions. The relevant scenarios to consider may become quite complex, for example when exploring the potential impact of using a new treatment in combination with diagnostic tests, monitoring biomarkers and treatment stopping rules. For a budget impact assessment, payers will certainly be interested in how many patients will be eligible for treatment with this new product and the quality of the evidence available to support this estimate.

Generally, we can anticipate limited data will be available and there will typically be substantial uncertainty when projecting long-term outcomes. If the model design discussions are initiated early, this can sometimes facilitate identifying the key data gaps to address and allow us to explore the feasibility of conducting additional studies to support the HTA submissions.

CONCLUSION

There has been tremendous scientific and clinical innovation that has driven a remarkable uptake in the number of orphan drugs coming to market in the past decade, and this has offered tremendous clinical, humanistic benefits to patients and families. So now the job of those who are working in market access is to be equally innovative and creative in order to develop the evidence to support value propositions and communications with healthcare decision makers to maximize patient access to these potentially transformative therapies.

For more information, please contact Thomas.Rising@evidera.com, Alex.Ward@evidera.com or Karen.Sandman@evidera.com.

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Methods for Selecting and Measuring Endpoints that are Meaningful to Patients in Rare Disease Clinical Development Programs

Margaret Vernon, PhD, Senior Research Scientist and European Director, Outcomes Research;
Kathleen Wyrwich, PhD, Senior Research Leader, Outcomes Research

The number of targeted treatments in the pipeline for rare diseases has nearly tripled compared to a decade ago.[1] The current and exceptional integration of several factors contributes to this rapid growth of treatments and cures in this arena. Genomic intelligence and associated therapeutic methods are ever-increasing, and pharmaceutical corporations, eager to build on this expanding knowledge, are de-emphasizing their former blockbuster model in favor of increased rare disease solutions. In addition, electronic medical records offer improved capabilities for data analytic methods to find specific rare disease needles in large database haystacks. This, in turn, improves opportunities for greater understanding of their genomics, biomarkers, symptoms, treatments, and ultimately, outcomes.

Stakeholder groups, including regulators, payers, policy makers, and patients, have demanded patient-centeredness in rare disease drug development programs. Patient-centered outcomes research has been defined as, (research that) "helps people and their caregivers communicate and make informed healthcare decisions, allowing their voices to be heard in assessing the value of healthcare options."[2] More specifically, the Patient-Centered Outcomes Research Institute (PCORI) and the U.S. FDA Center for Drug Evaluation and Research have discussed the importance of evaluating disease manifestations that are *important* to patients in rare disease drug development programs.[3] Furthermore, in a comprehensive review of orphan drugs submitted for health technology assessment (HTA) in Europe, Lyons et al.[4] found that HTA bodies regularly requested data from patient-reported health-related quality of life (HRQL) assessments included in clinical trials; Germany and France emphasized outcomes that would demonstrate clinical relevance of interventions to patients. Key decision makers in both the U.S. and Europe, and elsewhere around the world, are placing emphasis on outcomes *important* to patients in evaluation of orphan drugs.

Thus, patient-centered outcomes, most recently defined as, "those outcomes important to patients' survival, function, or feelings as identified or affirmed by patients themselves, or judged to be in the patients best interests by providers and caregivers when patients cannot report for themselves,"[5,6] are critical for inclusion as endpoints in rare disease drug development programs. However, the methodological challenge in developing outcome measures capable of achieving this definition's intent include: 1) defining endpoint concept(s) that are meaningful to patients, and 2) selecting endpoint concepts and measures of these concepts that are hypothesized to demonstrate a treatment effect, taking into account treatment mechanism of action, patient population included in planned clinical trials, and clinical trial design factors. This article focuses on the first challenge of identifying the endpoint concept(s) that are most meaningful to patients.

A key aspect of enabling optimal patient-centered endpoint strategy for clinical development programs is an early initiation of the necessary background research and endpoint planning, preferably prior to Phase 2 studies. Including the appropriate patient-centered outcomes in Phase 2 studies provides all stakeholders in the rare disease treatment program—patients, their caregivers, investigators, the drug development team, regulators and payers—with first-hand knowledge on the treatment effect measured with these endpoints. Moreover, the learnings from a Phase 2 clinical trial,

in conjunction with regulatory and payers' feedback to the endpoints and results, provides the opportunity for: 1) further improving the endpoints, if fine-tuning is indicated, and 2) a re-prioritization of the endpoints in advance of Phase 3.

A focused literature review of patient- and caregiver-burden and relevant HRQL concepts, as well as an examination of known published reports and recent conference abstracts from other outcomes measures used in prior clinical and observational trials, can provide initial information that is essential throughout the endpoint strategy and selection process. Second, the wisdom from clinicians experienced in treating patients with the specific rare disease can provide invaluable knowledge regarding the relevant disease signs, symptoms, and impacts of these symptoms on patients' lives. Moreover, clinicians with experience in other rare diseases that are very similar to the investigated condition can also offer insights on outcomes that have demonstrated patient-centered benefits in prior clinical trials.

However, in order to determine which improvements in the signs/symptoms or impacts of disease would be most meaningful to patients, patient and/or caregiver engagement is critical and necessary to inform endpoint selection. Yet traditional methods for gathering early patient input, such as focus groups, are very often impossible in rare disease populations due to the nature of rare diseases. By definition, there are few patients with the disease, and there is often a large geographical spread in the scarce number of persons with a specific rare disease. Further, rare diseases often include pediatric populations who either cannot report for themselves or may not reliably report using traditional focus group methods.

Innovative methods to gather patient input regarding meaningful endpoint concepts and measures are essential in rare disease clinical development programs. In early planning, one option for gathering information about important outcomes for patients is to use existing data available directly from patients and patient advocacy groups within a given disease area. Rare disease patient advocacy groups bring passion, enthusiasm, and dedication to assist in achieving this input, and Evidera's frequent opportunities to work with the champions continues to be a remarkable and moving experience. These patient advocates are well connected and tireless in their efforts to seek solutions. At the same time, they are painstakingly cautious in protecting the best interests of all individuals in their organizations.

With this important asset in mind, several other examples of publically available sources are provided below; each can be tailored to many specific rare diseases to provide insight on the patient experience and potentially meaningful endpoints.

- A review of patient discussion boards can provide insights into the important impacts of a disease from patients' perspectives as the patients and their caregivers discuss the day-to-day learnings, new treatments/devices and best ideas for coping with their condition.
- An examination of the reports from patient advocacy groups can provide information regarding endpoint concepts that are important to patients. For example, the Cystic Fibrosis Foundation Patient Registry Report is specifically designed to "identify new health trends, recognize the most effective treatments and design clinical trials for potential therapies."[7] (This registry includes data from 27,000 patients who receive care at accredited centers, and reports are available to researchers.)
- An appraisal of key learnings from some rare disease foundations who have joined forces with parent and patient advocates, clinicians and academic research teams, industry, non-profit organizations and/or government in drug development for a specific rare disease. Having invested in useful research tools, these foundations can greatly assist in understanding key endpoints for inclusion in clinical development programs.

Depending on what type of information is already available in the public domain, additional input from patients will most often be required to understand the full picture of outcomes meaningful to patients within the context of a specific disease area and therapeutic agent. Further, within many rare disease groups, there is a dearth of information regarding appropriate patient-centered outcomes in the literature or public domain. In all cases, gathering input from patients or caregivers themselves is essential.

The first challenge is identifying (enough) individual patients or caregivers/close family members to have confidence in generalizability of endpoint concepts identified as important. It is unlikely that placing general newspaper advertisements or recruiting through several clinical sites will yield enough patients to obtain generalizable results. Examples of innovative methods for identifying patients and gathering input regarding endpoint priorities are provided below.

- We have had success identifying patients to engage in early endpoint planning through partnerships with patient organizations, which often are typically interested in engaging in research that forwards patient-centered outcomes in clinical development programs. Patient associations may email their members study advertisements for opportunities to solicit input; the organization's newsletters, websites, and social networking sites (e.g, Facebook groups) are other venues where advertisements can be placed for study involvement.

- Rare disease scientific conferences often include sessions specifically conducted by patients/caregivers and other sessions designed for patient/caregivers, which assures attendance from patient/caregivers themselves. These conferences provide focused opportunities to recruit patients/caregivers for participation in discussions regarding their disease experiences and priorities for new therapies. These discussions can take place just before, during or immediately after the conference to accommodate patient/caregiver travel plans and their desire to participate in these opportunities to share their input.
- Some rare disease populations, especially those with an approved treatment, have organized disease registries, where patients with a confirmed diagnosis are registered within a database and engage in ongoing research activities. Adding research modules on endpoint priorities, input on patient burden, or other patient-centered outcomes to these databases may be an option to collect information from patients regarding patient-centered outcomes.
- Patients can be identified through on-line patient forums or chat/message boards for participation in research activities.

All of these options may have benefits and drawbacks, and the specific recruitment challenges within a given disease population as well as the research objectives should be taken into account and pros/cons weighed carefully regarding optimal recruitment strategy. Once an avenue for identifying patients to engage in early endpoint planning research has been identified, the next challenge is selecting the best methodologies for gathering input from a diverse and geographically dispersed patient population. Technology-enabled solutions can often address this challenge, and some useful examples are listed below.

- Telephone interviews allow for gathering of semi-structured qualitative patient input without the need for interviewers or patients to travel for interviews.
- Web-based surveys can be used to gather data from patients regarding treatment priorities; a modified Delphi panel technique might be used to gain consensus on endpoint priorities.
- Live on-line patient forums where a moderator posts a question and patients can reply to the question or comment on other responses is an interesting option to gather rich textual data on patient priorities.

In summary, inclusion of patient-centered outcomes in a rare disease drug development program is critical for market access success. Creative and innovative solutions to obtain patient input on treatment priorities are necessary when working in rare diseases due to the very definition of "rare disease." Reaching patients through non-traditional forums and utilizing technology solutions to gather patient input greatly reduces barriers to successfully engaging rare disease patients at this early stage in the drug development process. Including patient advocates and engaging patients throughout a program of drug development can also be enhanced by solutions outlined in this article. Indeed, the scientific challenges for rigorous health outcomes development and validation methods continue to require unconventional approaches and innovative methods because of the important limitations in rare diseases; yet the novel ideas that emerge provide valuable methodological insights for other disease area applications.

For more information, please contact Margaret.Vernon@evidera.com or Kathy.Wyrwich@evidera.com.

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Case Study: Developing a Condition-Specific Utility Measure

Dennis Revicki, PhD, Senior Vice President, Outcomes Research;
Anne Rentz, MSPH, Research Scientist, Outcomes Research

Utility and health preference measures are used to value health outcomes of interventions for clinical studies and cost-effectiveness analyses. When valuing the outcomes of certain treatments, sometimes generic health preference measures may not be the best choice. For example, a key challenge for most generic measures, such as the EQ-5D and the SF-6D, is that they do not completely capture the variations in outcomes for ocular conditions. Evidera and a team of individuals from industry and academic centers developed a new health preference measure designed to assess utilities for ocular conditions. We developed an approach for estimating health state utility scores based on responses to the NEI Visual Function Questionnaire 25 (VFQ-25)—the VFQ Utility Index (VFQ-UI).[1,2]

NEI VFQ-25 data from patients with central or peripheral vision loss were used to identify subsets of items covering important concepts underlying vision-related functioning. A Rasch analysis was performed to identify the subset of items representing varying severity levels for both peripheral and central vision loss. The Rasch analysis examined unidimensionality of the responses, using item fit statistics, threshold maps, category probability curves, and item characteristic curves. NEI VFQ-25 data from multiple central vision loss and peripheral vision loss studies were used for these analyses (n~3,000). The data were examined separately, identifying items that best fit each type of vision loss. Finally, we combined the datasets to identify the final set of items that had the best psychometric properties for both central and peripheral vision loss. The final selected NEI VFQ-25 items are summarized in *Figure 1*.

Health states based on the selected items were developed to represent the range in vision-related functioning. These health states were then valuated with a time trade-off procedure using members of the general public in Australia, Canada, the United Kingdom and the United States. Approximately 150 participants were interviewed in each country. Finally, the multinational valuation dataset was analyzed to create the VFQ Utility Index scoring algorithm.

FINAL ITEMS & CONCEPTS FOR VFQ-UI HEALTH STATES	
Item	*Concept*
See well up-close	Near vision
See people's reaction to things I say	Vision-specific social functioning
Going out to movie, play, sports event	Distance vision
Limited work time due to vision	Vision-specific role difficulty
Stay at home because of eyesight	Vision-specific dependency
Worry about doing things that will embarrass me or others	Vision-specific mental health

figure 1

A complex series of analyses were completed since the different concepts reflected in the selected items were partially dependent on each other. We applied item response theory (IRT) analyses to obtain an indicator of severity for each health state defined by the VFQ-UI classification system and then mapped the severity indicator onto the utilities of targeted study health states. First, we used the data set from Phase 1 to estimate severity (theta) scores from the patient-level responses to the six VFQ-UI items using a graded response model. Theta represents the location of the health states in terms of vision-related function, where higher scores indicate better functioning. Regression models were then conducted to map the relationship between time trade-off (TTO) preference scores and selected demographic variables and VFQ-UI thetas. Different regression models were explored to determine whether linear or nonlinear regressions represented a better fit in estimating TTO scores. These regression analyses were then used to estimate the utility score, and an equation was established for estimating utilities based on responses to the six items on the NEI VFQ-25.

The investigators in the National Health Measurement Study evaluated the one-month change in different generic health preference scores (i.e., SF-6D, EQ-5D, QWB-SR, HUI2, HUI3) after cataract surgery.[3] Cataract surgery usually results in a very large improvement in visual acuity and very good vision-related functioning outcomes in most patients. Since the NEI VFQ-25 was also included in this study, the VFQ-UI was scored and separately analyzed. Based on the results, the SF-6D, EQ-5D, and QWB-SR all demonstrated very little change after one month, with standardized response means ranging from essentially 0 to 0.15. The HUI2 and the HUI3 showed some responsiveness (0.22–0.25), mainly because there are items covering vision problems in those two preference measures. The VFQ-UI was fairly responsive with a standardized response mean of 0.36, and the NEI VFQ-25 was the most responsive with a standardized response mean of 0.77, since it is a very comprehensive measure of vision-related functioning.

In conclusion, an algorithm for converting VFQ-UI scores into health preferences was developed. This vision-related preference score is expected to be more responsive to differences among the effects of ophthalmologic interventions than generic health preference measures. The VFQ-UI represents the patient's perspective on the impact of ocular conditions on functioning and well-being, and VFQ-UI scores allow for comparisons across ocular disorders. These VFQ-UI scores may prove valuable for comparing different vision-related treatments and for estimating quality-adjusted life-years (QALYs) for economic evaluations and health policy decisions.

For more information, please contact Dennis.Revicki@evidera.com or Anne.Rentz@evidera.com.

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Negotiating Patient Access—A Matter of Culture and Stamina

David Alderson, MBA, MEng, DipM,
European Practice Lead, Payer Research and Strategy

It seems like the global economy is slowly turning back to positive growth, with a solid start to 2014, pointing to a quarterly gross domestic product (GDP) expansion of three percent.[1] But as it takes time before increasing GDP fuels public and social security budgets, and reversal of various cost containment policies is unlikely, we may be looking at several difficult years still ahead. Hence the life sciences industry will need to continue to focus on patient access as a core element of their business and product strategy, and for commercial success, marketing plans will need to address the thinking and decisions of payers, on a national, regional and hospital level.

Payers are very aware of their power position in these days of austerity. A participant at a recent negotiations training commented: "Payers want everything these days. First a superiority trial versus standard of care that proves your product is worth the budget. If you are so lucky to have this, they will ask for real-world data proving you can beat standard of care in daily practice. If you have this data, they will search for the most optimal patient segment and restrict patient access that way."

It is naive to assume payers use strict guidelines, rules, and regulations so they can unequivocally decide about reimbursement and fair pricing. From experience it is clear there are many more subjective elements that feed into a final decision. Payers cannot afford clear decision criteria as this might create conflicts with budget control. Moreover, they need the flexibility to handle the political aspects that go hand in hand with many important access decisions. As Gavin Kennedy said in his famous book, "Everything is negotiable".[2] This also seems to hold true in patient access and is endorsed by many unexpected positive and negative outcomes of market access business cases.

Therefore an important part of the overall market access tool kit, alongside value communication, evidence, decision processes and stakeholders, is how you negotiate and communicate. So, what type of negotiation skills would help achieve and optimize patient access for a novel product?

The answer to this question starts with better understanding of what a negotiation is all about. Most definitions are quite broad, such as, "to negotiate is to work or talk (with others) to achieve something" (a transaction, an agreement, etc.).[3] Given this definition, many negotiation opportunities can be recognized in market access, although decision makers (e.g., Minister of Health and Managing Director) may actually never meet face to face.

PATIENT ACCESS NEGOTIATIONS MAY HAPPEN ON ALL LEVELS AND AT ALL TIMES, INCLUDING:

- Discussions with payers about the best ways to develop products
- Scoping discussions with health technology assessment agencies
- Discussions about therapeutic value and position in the treatment pathway
- Price and reimbursement negotiations
- Discussions about patient access schemes
- Pre-tender and contract negotiations
- Discussions about price modulation and other cost containment measures

A company that has a number of products on the market may find itself negotiating with payers almost continuously, so maintaining an excellent relationship with payers becomes critical—even during tough discussions. Therefore, companies that have developed good internal negotiations skills have all opted for the so-called integrative or collaborative negotiations approach. This approach assumes that there is potential for both parties to create joint value, i.e., achieve a win-win outcome.[4] For many, this implies a change from the hard bargaining model to a more gentle mentality. It also intimates recognition that payers are not against innovation in an effort to control costs, but that they realize the importance of treating patients with innovative treatments. Keeping good products out of the market may lead to negative press, political pressure, and decreased innovation—all of which are undesirable for payers. This was illustrated recently when the Committee for Reimbursement of Medicines (CTG-CRM) in Belgium was at the center of a news story covering a patient that died because a certain treatment was not reimbursed and his family could not find the money for timely treatment. The story did not focus on the manufacturing company or the price but rather on the legitimacy of not allowing the product in Belgium while it was reimbursed in neighbouring countries.

There is no "one size fits all" best practice, but it is important that successful negotiating is built into both the company and market access planning. The following outlines a range of workshop-based approaches that have contributed to success. These have been developed and optimized over the years through working with both payers and companies.

There are three broad areas of this focus.

1. Training in negotiation and communication skills. *(Capability Building)*
2. Product specific preparation for negotiating market access or tendering conditions. *(Launch Preparation)*
3. Support in actual market access negotiation cases. *(Implementation)*

Within each area there are a number of workshop-based approaches, but outlined below are some examples of typical projects in these areas.

A. Global Value Dossier Roll-Out Workshops

The principle use of Global Value Dossiers (GVDs) is well established. Their success, however, does depend on effective roll-out to affiliates and local adaptation, and the efficient translation of understanding to those involved in local access negotiations.

There is significant synergy between developing the GVD and ensuring its effective adaptation and integration

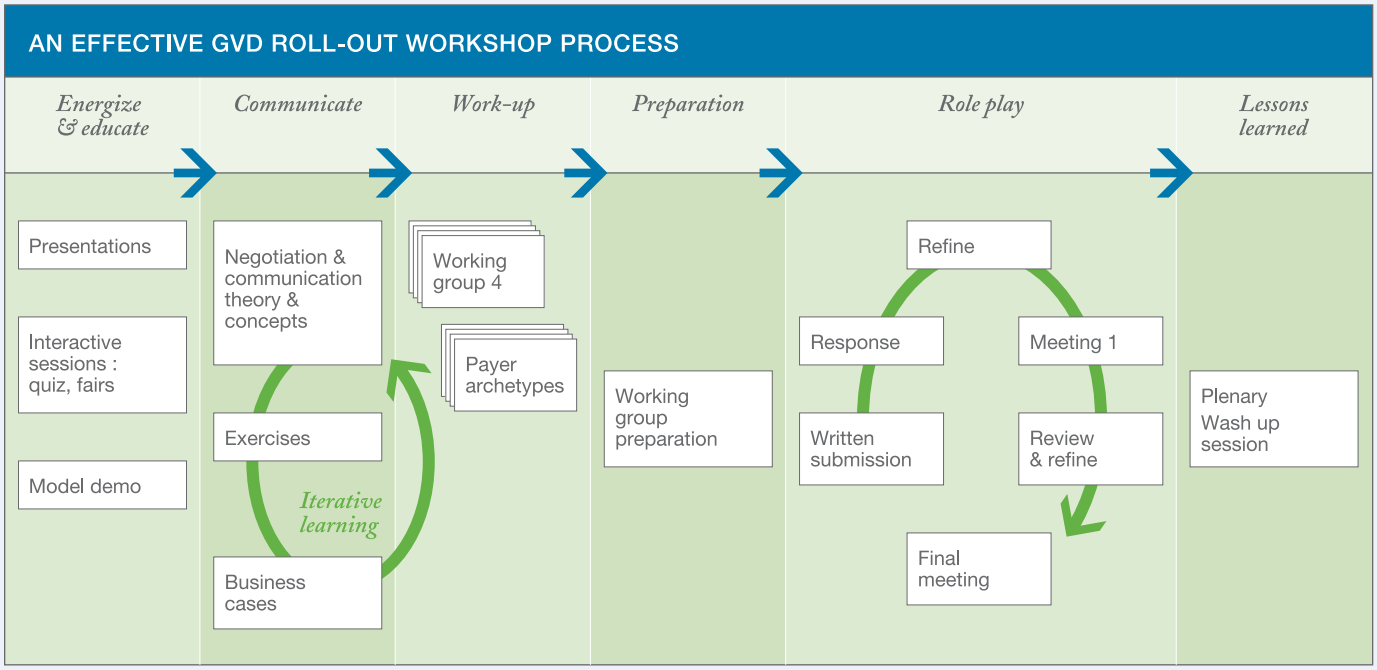

figure 1

at an affiliate level. Efficient roll-out not only focuses on the content of the dossiers, but includes training on the negotiation strategy that supports it. This negotiation strategy can seamlessly fit into existing internal negotiation cultures. (It is always important to ensure that negotiation strategy fits to the organization; trying to change the organization around a negotiating approach is not a successful recipe. Any consultant partner should have experience with many collaborative negotiation approaches and be able to adapt these workshops to the predominant company culture and organization.)

A global value dossier roll-out workshop starts with education on the global market access strategy—this may include presentations, education fairs, quizzes, cost-effectiveness (CE) model demonstrations, etc. It has been found helpful to next repeat or introduce collaborative negotiation and efficient communication concepts, in a mix of short exercises, ongoing business cases, and some theory. Participants are subsequently split into working groups, each of these targeting a relevant payer archetype. The working groups prepare a negotiation strategy and tactics for realistic payer negotiation cases and these cases are role-played, with surrogate and sometimes even real payers as the other party. As in the real world, the negotiations are iterative, and mimic each step—from the written application until the concluding meeting. The workshop ends with a plenary discussion of lessons learned, strengths and weaknesses of the market access strategy. Frequently this discussion also yields to updates to the global value dossier content and objection handler.

Flexibility is key. The scope of such roll-out workshops is flexible. Some companies may opt for one workshop; some others prefer a series—each covering different geographies. Some companies expect a negotiations script that can be shared with others facing the same circumstances. Others target case-by-case in-market support. Some companies run all workshops in English, whereas others prefer local languages—with or without translations. It is important that the workshop provider has the expertise and capabilities to handle this broad spectrum of client preferences.

B. Tendering and Contracting Workshops

Another key workshop for negotiation support pertains to the tendering and contracting process that currently is used for hospital and generic products in many markets. These focus on the understanding of strategic and negotiation concepts, and complement trainings on the commercial and technical aspects of these procurement processes. As with the global value dossier roll-out workshops, these meetings are often spiced with fun exercises, real business cases and role playing. The key in these workshops is to strive—in close collaboration with the client—to produce exercises and role plays that are as close as possible to the real thing. It is a measure of success to get the spontaneous remark of participating key account managers that "it felt like real."

C. Capability Building

One-shot training workshops are like a stone in the water—they create a wave of awareness, but ultimately the water will return to its status quo. Therefore, ideally the concept of a market access negotiation culture is created. To that end, a spectrum of activities should be considered, going from one-day awareness workshops, up to full-week, in-depth negotiation champion trainings. Also helpful is supporting this culture change with templates and tools that are fine-tuned

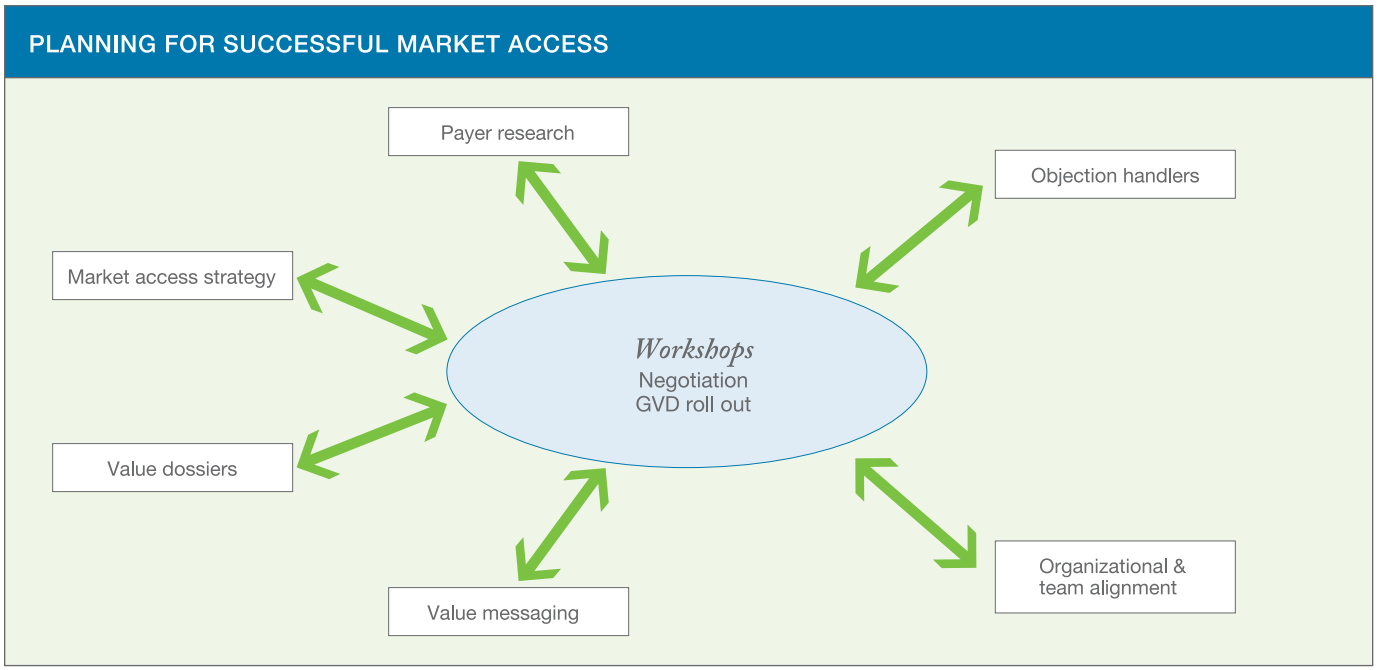

figure 2

to the company image and requirements. It takes time, but in the end, investing in a well thought out market access culture will allow a company to create many stories of positive outcomes in market access negotiations.

D. Implementation

Training workshops are fun and they are very gratifying for the trainers when met with positive feedback. But the proof of skills and theoretical approaches can be found in the real negotiations. These negotiations may focus on new patient access schemes, or aim to defend pricing and reimbursement of incumbent products, or focus on countries where pricing approvals are lagging behind. In these cases, strategic partners should work with companies as one team with the local company experts to identify issues, brainstorm options and alternatives, and develop a strategy. A useful element here is insights from analogue cases, in other therapeutic areas or geographies, drawn from previous experience.

The combination of training capabilities, sound theoretical knowledge and active support in real cases, together with unsurpassed payer expertise, provides both the theoretical, educational and business keys to success in negotiation support. Aligning these to other activities—payer research and strategy development, and development of value messages, dossiers, and objection handlers—creates significant synergies and successful market access *(see Figure 2).* In conclusion, the use of workshops can provide a foundation to ensure optimal alignment and implementation within an organization and so lead to improved market and patient access.

For more information, please contact David.Alderson@evidera.com.

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Accountable Care Organizations: Evolution of Care Delivery and Provider Compensation in the U.S.

Mike Epstein, MSc, Director, Market Access

"How can the best medical care in the world cost twice as much as the best medical care in the world?"[1]

Dartmouth Professor Elliot Fisher asked this question at a 2006 meeting of the Medicare Payment Advisory Commission on regional variation in spending and outcomes. Fisher pointed out higher spending regions fail to deliver higher quality care. As redress for a fee-for-service system that rewards volume without regard to quality or cost, Fisher suggested the formation of what he called "accountable care organizations (ACOs)." He envisioned ACOs as groups of providers charged with population health management, compensated according to the value of care (defined as $^{Quality}/_{Cost}$) rather than its volume.

Four years ago, the Affordable Care Act put money behind the ACO movement, offering ACOs a share of any savings they could generate among Medicare beneficiaries. Since then, roughly 500 ACOs have emerged.[2] The movement has expanded well beyond Medicare ACOs to include commercial and Medicaid ACOs. ACOs serve 1–10% of the population in a majority of states, up to a maximum of 25% in Oregon.[3] By one estimate, ACOs currently serve between 37 million and 43 million patients.[4]

As with any organizational evolution, ACOs have changed beyond the "extended hospital medical staff" envisioned by Fisher. ACOs today may be comprised of medical groups and may not always include hospitals. Moreover, ACO sub-types have emerged and include Totally Accountable Care Organizations (TACOs), which are Medicaid ACOs that provide medical care but also mental healthcare, substance abuse treatment, and social supports addressing problems like homelessness.[5]

Amidst all the media attention, pharmaceutical and device manufacturers are asking three questions about ACOs.

1. Are ACOs here to stay?
2. What impact should I expect for my products?
3. What can I do to successfully navigate the ACO environment?

1. ARE ACOs HERE TO STAY?

Probably the best approach to this question is to ask a slightly different one: are ACOs just thinly disguised versions of their HMO cousins, doomed to the same failures of the early 1990s? Detractors have made this case, yet if ACOs fail, it won't be for the same reasons as HMOs.

First, ACOs are compensated differently from HMOs. HMOs were paid via capitation without any meaningful quality-based metrics tied to the capitated rate. Just as fee-for-service promotes overutilization, capitation promoted underutilization. If ACOs are too frugal with care, it may impact the quality measures. Furthermore, as ACOs are geography-based, rather than employer-based, the patient population is not expected to change rapidly, so ACOs will likely retain populations for longer than traditional insurance plans.

Second, computer technology and the ability to monitor metrics have far outpaced that used by HMOs of the early 1990s. An efficient Electronic Health Record (EHR) system is a *sine qua non* for a successful ACO. EHRs allow the real-time data sharing and access to sophisticated clinical decision support tools ACOs need in order to fulfill their promise of better care coordination. Having pathway models and these tools at providers' fingertips can help keep them "on pathway" and allow sophisticated analyses, such as risk stratification, to identify high utilizers for focused intervention.

EVEN IF ONE ACCEPTS THAT ACOs ARE MEANINGFULLY DIFFERENT FROM HMOs, THERE ARE MANY HURDLES ACOs MUST OVERCOME TO FIND SUCCESS AND, ULTIMATELY, LONGEVITY.

Third, patients do not join ACOs as they did HMOs, and many are not aware that they are in ACOs. Rather, their providers join ACOs. Without the affirmative requirement to join, patient awareness that they are managed by providers in an ACO will likely remain low. This lack of awareness reduces the odds of patients resisting the structure.

Fourth, a key source of patient complaints during the HMO revolution was payers' authority to restrict patients to particular providers. Unlike HMOs, ACOs are not empowered to restrict patient choice in this way. For example, a patient served by a Medicare ACO may see any provider who accepts Medicare—regardless of whether the provider participates in the ACO.

Even if one accepts that ACOs are meaningfully different from HMOs, there are many hurdles ACOs must overcome to find success and, ultimately, longevity.

Technology

One challenge concerns the same technology that will drive ACOs' success. EHR systems are produced by different manufacturers who do not necessarily make their systems compatible with one another. Providers within an ACO may not be using the same EHR system. Just as problematic, the ACO's EHR may not communicate with systems used by all of the ACOs' third-party payers. If the ACO cannot use its system to effectively coordinate care, that part of the ACO value proposition collapses. The Office of Standards and Interoperability at the Department of Health and Human Services recognizes this challenge and is working to ensure that EHR systems can communicate with one another.[6]

Incentives

Incentives pose the second major challenge for ACOs. The expectation is that ACOs will be paid via risk sharing. The Medicare Shared Savings Program was set up to phase in risk sharing during later years; however, it began with shared savings or the positive incentive for risk sharing. Most initial commercial ACO contracts are also limited to the upside potential only. Payers and ACO executives have indicated there is a simple reason for this: providers are loath to adopt downside risk before proving the risk is minimal. Related to this is the financial potential. Will physicians change the way they practice for a bonus that may represent 2% or 3% of income? What about 5%? How much is enough to change providers' behavior?

Tracking Utilization

Patients have the right to decline sharing of their personal health information among ACO's providers. ACO executives are concerned about this, increasingly so after data breaches among the recently launched healthcare exchanges. It is conceivable that the public will decline to grant ACOs permission to share their data in sufficient numbers to allow ACOs to reach their potential in oversight of a population to determine interventions that will improve health.

Even when patients consent to have their data shared within an ACO, the ACO may not be able to track patients as thoroughly as necessary. The best example to date concerns ACOs that lack hospitals and thereby have difficulty tracking hospital admissions. Inability to accurately track utilization will make calculation of performance, and ultimately payment, difficult, if not impossible.

2. WHAT IMPACT SHOULD I EXPECT FOR MY PRODUCTS?

As their time horizons lengthen, ACO executives will be focused on the prevention of use of more intensive services and early intervention, as well as evidence-based medicine. ACOs are investing heavily in case managers and hospital discharge planners to keep patients healthier and ensure care transitions are smooth. In addition, there is growth in the use of clinical pathways.

ACOs are using clinical pathway models in a variety of categories, from oncology and cardiology to rheumatology, neurology, and pulmonology. Pathway models have expanded beyond therapies into diagnostics, putting pressure on diagnostics manufacturers in addition to pharmaceutical and biotech companies. While clinicians are not prohibited from prescribing/ordering off pathway, compliance is reported to be extremely high because compensation is tied to behavior. The hurdles are high and becoming higher for off-pathway technologies.

Bundled/episodic payment in some categories is putting price pressure on a variety of products and services and further supports the use of pathways. This type of compensation previously was limited to transplants and labor and delivery. There is, however, increased focus on areas where variation in quality and cost are high, particularly orthopedic procedures such as knee and hip replacements.

Overall drug use is expected to rise as ACOs seek to shift appropriate cases from the surgical theater to the office setting to reduce costs. The mix of drugs is likely to shift as pressure to prescribe generics and biosimilars, which is already strong, gets even stronger. Use of clinical pathway models supported by clinical decision support tools, with compensation tied to prescribing decisions, is expected to facilitate this shift.

3. WHAT CAN I DO TO SUCCESSFULLY NAVIGATE THE ACO ENVIRONMENT?

To successfully access the ACO market, manufacturers need to invest heavily in clinical, economic, and humanistic **evidence generation**. ACOs demand evidence that drugs, devices, and diagnostics have positive impact on the value equation. This means boosting the quality of care, reducing the cost of care, or both. Less than budget impact, ACOs are looking at **value impact**.

Communication regarding a new therapy's value proposition will be key as ACOs seek to invest in technology that helps them shift care out of the hospital and into the home or office, and prevent rather than acutely treat. Manufacturers of home healthcare and tele-health technologies, as well as evidence-based screening and diagnostic tools, have a clear message to which ACOs should be receptive, while manufacturers of chronic care therapies will need to emphasize the impact of disease management and adherence programs for the ACO's population over time.

Just as the HMO revolution changed managed care, the ACO movement will permanently change provider behavior. Manufacturers developing a new therapy are best served by providing the evidence to support the value proposition and clearly communicating what that means in terms of a populations' health.

For more information, please contact Mike.Epstein@evidera.com.

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So What Exactly is Your Real-World Data Strategy?

Rob Thwaites, MA, MCom, Vice President, Health Economics and Epidemiology

Fail to prepare… and prepare to fail. This risk hangs over drug companies without a planned approach to using real-world data to support the products they develop and attempt to commercialize. Why is such data crucial to success, and what should a company do to build a real-world data strategy?

Every new compound needs an evidence strategy, whether that is a stand-alone plan or an integral part of the overall commercial strategy for the compound. Behind the efforts to create the evidence is a need for data: synthesis of existing data; new clinical data; and new "real-world" data (RWD). New RWD is an increasingly important component of this package, particularly for filling gaps left by other sources. It is, for example, essential not only to inform internal, company decisions, where no guidance is available either from the literature or from earlier in-house research, but also to inform external, healthcare decisions on the use of a new product in clinical practice where no insights can be gained from the clinical development program.

All this means that collecting the real-world data efficiently and effectively is critical to the success of a new product as it moves through research and development into clinical practice. Investments in RWD studies can, however, be time-consuming, costly, and subject to various uncertainties. Companies can easily find themselves falling behind unless they plan ahead for data to be available in good time for decision making.

But there is another dimension to this. Ideally planning for RWD should apply not only to a given compound, but also for needs *across* compounds and *across* development programs. With a real-world data strategy that can support one or more compounds, a company can capture savings in time and cost (e.g., in acquiring and analyzing data), and through time can build its expertise in using the data for analyses that will, in turn, be more effective in meeting decision makers' demands for evidence.

DEVELOPING AND IMPLEMENTING A RWD STRATEGY

There are some examples of individual companies adopting approaches to RWD that support multiple products

or multiple departments, driven at least in part by the increasing demands from healthcare decision makers for evidence based on RWD. With the current excitement about "big data" and its possibilities in both healthcare and in life sciences, senior management is increasingly interested in exploring possibilities with data and in partnering with organizations that have already built RWD-related capabilities.

Over the last few years, a large biopharmaceutical company has built upon its existing in-house expertise in RWD by establishing strategic relationships with organizations with strengths in data and analytics. In 2011, the company and a health outcomes company launched a collaboration[1] to conduct real-world studies—prospective and retrospective observational studies on disease states as well as studies to compare the effectiveness of treatments—to support research for new compounds as well as for drugs already on the market. In the following year, the company went on to announce agreements with another private data provider and a public data provider in the UK (the Health and Social Care Information Centre).

The company's strategy does not simply rely on data and expertise from these three partners, as it continues to conduct and publish studies using its own expertise and with other collaborators for specific projects. Recently, for example, the company published results from a novel piece of work to link information across several different datasets in the UK (the MINAP and GPRD registries, the HES hospital data, and the ONS mortality data).[2] Overall, therefore, the company's RWD strategy supports multiple disease areas and is based on multiple collaborations.

This is only one example of a number of companies that have invested in strategic approaches to the use and development of RWD. In another large pharmaceutical company, for example, the R&D division has developed a RWD strategy focusing on capability building. While the company does have a centralized approach to in-licensing and accessing data, it has identified a widespread lack of awareness and skills in understanding how the data can be harnessed as a limiting factor in taking advantage of RWD. Building these capabilities is a long process, but interest is spreading within the company from those groups most familiar working with observational data, including Epidemiology and Health Economics and Outcomes Research (HEOR) to additional groups, such as Safety and Regulatory where there have been increased requirements from their stakeholders. Crucially, data needs are still driven by needs of individual brand teams and so the broader RWD strategy ties back to the evidence and commercial strategies for a particular product.

Companies are also looking for opportunities to help guide earlier research activities. Another large biopharmaceutical company recently acquired a company with success in identifying genetic risk factors in a range of diseases using detailed genetic and medical information from hundreds of thousands of individuals. The company expects that this will increase its ability to identify and validate human disease targets, in turn leading to efficiencies in drug development.[3]

BENEFITS OF A RWD STRATEGY

A RWD strategy can open up a range of benefits to a company, with studies using RWD—supporting activities across the breadth of the product lifecycle from research through development and post-launch—more easily conducted. A few examples are listed below.

- In research, the use of genomic, proteomic and clinical data to better understand diseases, identify targets and predict the likely consequences of treatments;
- In clinical development, new applications for evaluating protocol feasibility and identifying patients promise to cut recruitment times significantly from recent experience (example of an early pilot[4]);
- In pharmacovigilance, new technologies are allowing signals to be identified earlier and hypotheses based on outcomes in clinical practice to be generated sooner.

An important thing to recognize here is that a company does not have to have all the skills in-house—there are organizations that focus on specific capabilities and who can provide the services at lower cost and with greater expertise than if a company built the capabilities internally.

More broadly, by thinking strategically, companies can work together to harness the power of RWD in the future. Many of the underlying capabilities needed to process and analyze RWD are still in development and several companies have made a strategic commitment to contribute to multi-company or industry-level efforts, such as the recently completed Observational Medicines Outcomes Partnership (OMOP) in the U.S. and the range of ongoing projects relying upon electronic data under the Innovative Medicines Initiative (IMI) in Europe. Companies' investments in these activities form part of their long-term RWD strategy.

RWD STRATEGY—STILL UNCOMMON

Strategic initiatives to be more systematic and effective in the use of RWD are not new.

- Since the 1990s, payers in the U.S. have employed their internal data in retrospective research to understand, for example, patterns of utilization and associated costs for existing therapies and for modeling the impact of new therapies.
- In the early years of the last decade, a biopharmaceutical company launched its Healthcare Information

Factory,[5] bringing together IT experience, data sources and in-house analytical capabilities.[6] The company subsequently published many studies using the U.S. database cited, across a range of disease areas, and worked with data from a number of other countries.

Despite this, in our experience, such a strategic approach to building a company-level RWD capability is still the exception rather than the rule in industry. While there are many examples of companies successfully using RWD in projects to create evidence in support of a particular drug or device, we have come across very few documented, company-wide, RWD strategies. This is surprising, given that publicly available patient level data has been around for a couple of decades now and given the more recent excitement about "Big Data".

RWD STRATEGY—KEY FACTORS FOR SUCCESS

From the work we have done with clients, there are many lessons that we have learned and several critical insights into the design and implementation of a RWD strategy that we have gleaned. Design is not straightforward—there is no standard blueprint to work from—and implementation will take years rather than months. Outlined below are some of the critical factors that will lead to success.

- Define the scope of the strategy. Find ways to focus the strategy, limiting the area of the organization involved, or data types, or geography, to make the new approach manageable at the start.
- Secure engagement from the top. Ensure active and vocal senior management support for the strategy, as this will be essential for investment and for buy-in from others in the organization who will need to be involved in RWD activities.
- Develop champions at all levels. Work with those in the organization who understand the potential of RWD to help communicate the possible uses of RWD and overcome reluctance in project teams to consider RWD work.
- Use while you build. Communicate early 'wins' with the first data or partnerships to the company to highlight the value and win additional support.
- Establish partnerships. Actively seek out opportunities to work with others who have data, technology, or capabilities to take advantage of their strengths and to learn from their experiences and knowledge.
- Build and share capabilities. As this is a journey that will take time, foster the growth of the in-house skills and experience, and share this expertise across relevant teams within the company.

With the explosion in the availability of RWD, particularly in North America and Europe, life sciences companies are recognizing the many opportunities that these resources offer in research and development. In most cases the responses are piecemeal—the development organization commissions an epidemiology study to better understand the course of a disease and its treatment; the HEOR team commissions a chart review to understand treatment patterns and resource use to help with budget impact analyses; the commercial function commissions a database study to understand adherence patterns with a recently launched drug. Few companies have begun to consider how to engage across multiple parts of the organization or to invest in capabilities to capture the opportunities that are emerging from newer data sources. A dedicated RWD strategy can provide the framework not only for investments in the capabilities needed but also for encouraging groups across the organization to plan for greater and more effective use of RWD.

For more information, please contact Rob.Thwaites@evidera.com.

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Increasing the Value of Database Research with Validated Coding Algorithms

By Matthew W. Reynolds, PhD, Vice President, Epidemiology

The employment of high quality methods for retrospective database research has never been more clearly relevant and important given today's pharmaceutical research environment. An analysis from 2010 shows a significant increase over time for claims database *(see Figure 1)* and electronic medical record (EMR) database studies *(see Figure 2)*. Although the analysis has not been updated with data from 2011 to the present, the expanding focus on the use of retrospective databases suggests the continuation of this exponential increase. We have seen a tremendous effort in the design of large safety-based database initiatives in the United States (e.g., Sentinel Initiative) and Europe (e.g., EU-ADR), as well as the creation of groups like the Observational Medical Outcomes Partnership (OMOP) which have focused many of their efforts in the area of epidemiological and safety-based database research methods. One of the areas of particular interest for these groups has been the identification and development of validated coding algorithms for use in identifying and defining study cohorts, health outcomes of interest, as well as patient comorbidities. Validated coding algorithms are important for a couple of reasons. First, the process of defining them has not always been as rigorous as desired (or well published), leading to incorrect identification of patients, misclassification of events and costs, and inaccurate research results. Secondly, there is an opportunity to leverage the expansive number of databases available today, with access to tens and sometimes hundreds of millions of patients, to meet regulatory requirements. Increasingly, regulatory agencies in both the U.S. and Europe are allowing the use of these databases in a rolling retrospective way to meet post-marketing commitments that historically would have had to be done through registries or chart reviews.

A coding algorithm can be defined as a combination of diagnosis, procedure, drug, or lab value codes (e.g., ICD-9, CPT-4, NDC) and/or conditions (e.g., diagnostic code in the primary position of a hospital claim, minimum length of stay in a specific care setting) that can be used to identify a specific clinical term in an electronic healthcare database. Hence, all key clinical variables in a database study would be defined via coding algorithms. Some may be simple (e.g., a single diagnosis code), while others could prove notably more complex (e.g., a diagnosis code in a primary hospital position within 30 days of a second diagnosis code). All these clinical variables would be expected to be defined and operationalized prior to conducting the associated database analyses.

THE OPTIMAL APPROACH FOR CONDUCTING HIGH QUALITY DATABASE RESEARCH WOULD INCLUDE THE IDENTIFICATION, ASSESSMENT, AND INCORPORATION OF VALIDATED CODING ALGORITHMS INTO THESE DATABASE STUDIES.

In most publications using claims or EMR databases, the authors rarely provide full descriptive definitions for how the key variables were operationalized and how those definitions were determined. It is more common that an author may provide some definition for the study cohort of interest and/or the key health outcome of interest, but rarely are other clinical covariates ever defined. Further, while it may be more common to define the cohorts and health outcomes of interest, it is rare that the authors note how and

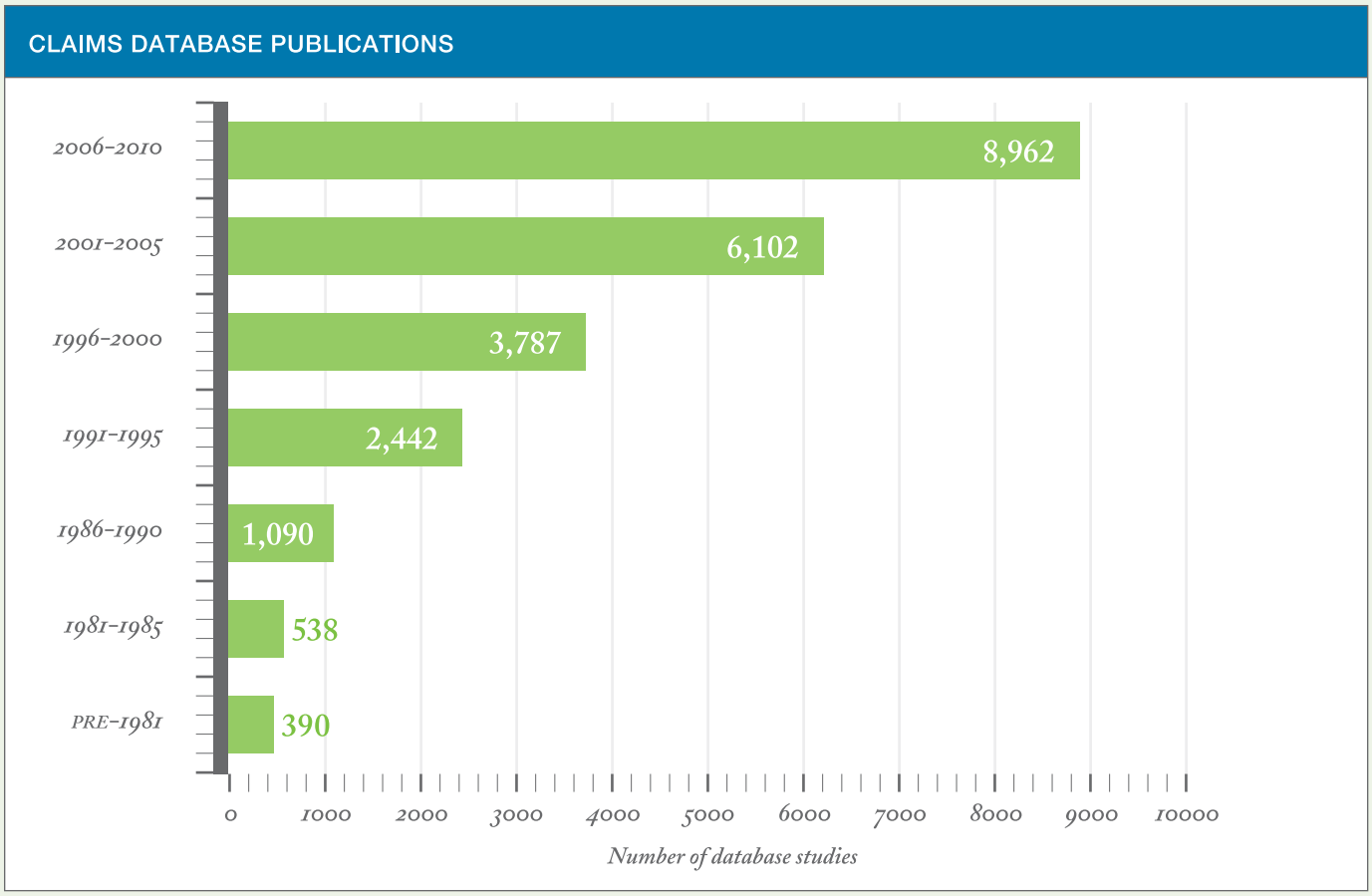

figure 1

why the definitions were determined or developed. This becomes a major issue when attempting to determine how to compare results from multiple database studies that clearly utilized different definitions for their key variables and/or never defined their key variables at all. While many databases clearly require variations in coding due to the inherent differences in the underling coding systems (e.g., ICD-9 vs. OXMIS), the coding variations across studies limit our ability to quickly detect important patterns in the natural history of disease, and they further impede our ability to reach defensible conclusions about the safety, effectiveness, and cost-effectiveness of existing treatments.

The optimal approach for conducting high quality database research would include the identification, assessment, and incorporation of validated coding algorithms into these database studies. Employing knowledge from similar, published database studies that demonstrate the effectiveness, or lack of effectiveness, of various coding algorithms for specific clinical events would help to assure that database studies are accurately and completely identifying the appropriate clinical events of interest. Using information about the positive predictive value (PPV—the proportion of positive results that are true positives), sensitivity (the percentage of people correctly identified as having the condition being studied), and specificity (the percentage of people correctly identified as not having the condition being studied) of various coding algorithms would help to drive the decisions about how best to define the clinical events of interest in each database study. Ideally, a score of 75% or higher in all three areas is desired for optimal results. To highlight this importance, in August 2010, the Database Special Interest Group for the International Society of Pharmacoepidemiology (ISPE) conducted a workshop to provide guidance to database researchers regarding the identification, development, validation and translation of coding algorithms in electronic healthcare databases.

The literature is the first place to start when identifying the best coding algorithm to use when defining clinical terms of interest. A very clear list of clinical terms should be created, including disease, terms of interest

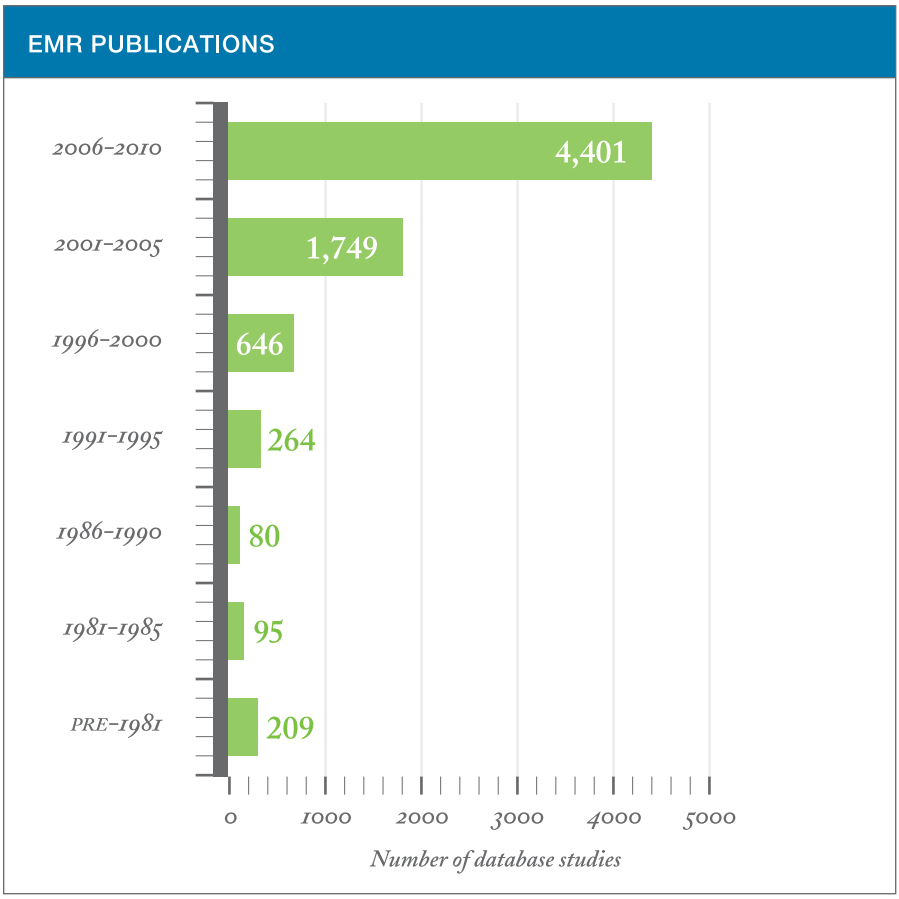

figure 2

and study types, and it is important to be as specific as possible since the coding algorithms that are built are typically going to tie to a very specific clinical event of interest. Focusing on claims and EMR databases will help narrow the search strategy, however, this can be challenging since EMBASE and MedLine only recently established good search terms for databases and PubMed still has not. Limits and criteria need to be thought through very carefully. When considering how far back to look, consider things such as how valid an algorithm from 10 years ago would be now, or have treatment patterns and definitions changed? It is also important to note that peer-reviewed publications may not be plentiful in this area, so conference abstracts should also be considered since better results may be found here as opposed to published articles alone. A screening strategy then needs to be developed to identify which studies should be used and which should not. Typically, any database study that has the specified clinical term of interest with clear definitions would be kept and then prioritized. The best studies are those that have used the database of interest and include a detailed coding strategy along with validation metrics. References from publications can also be explored to further expand the possibility of viable studies. Contacting authors directly is another option to identify codes used in previous studies.

When there is nothing in the literature, validated coding algorithms need to be developed from scratch. Past studies from the literature can be assessed to see which codes were used, even if they were not validated. Medical coders can provide insight into which codes are typically submitted for reimbursement for specific diseases and treatments. Clinicians can provide valuable insights, such as how commonly they use particular codes in their practice. The clinical insight is invaluable to better understand the patient evaluation, diagnosis, referral, and treatment patterns which will drive the engineering of optimal coding algorithms. Knowing factors such as the place of service, the physician type and timing between codes/visits can be instrumental in the building of coding algorithms.

Given the difficulty in identifying and synthesizing this evidence, combined with a desire to ensure consistency of definitions across studies, some industry groups, such as the Pharmacoepidemiology and Database Research Unit at Merck and Company, have developed a central coding library based on literature and clinical expertise to support their clinical and epidemiology research needs. Groups like OMOP have explored a variety of ways to best identify all available information on coding algorithms and how best to employ them consistently across databases.[1]

Validation of an algorithm can be very complex, but basically, once an algorithm is built, it needs to be shown that is really works. Does it actually identify the patients needed? Does it discriminate between cases and non-cases? Validation requires a gold standard to define the case. Most published studies have required chart reviews, but more commonly, EMR databases can also be used to create an algorithm based on components from both billing interactions and clinical chart/text information. The key is being able to reliably identify true cases and non-cases to build a validated coding algorithm. Think through and analyze your algorithm and then apply it. Calculate the PPV, sensitivity, and specificity to see if any modifications to the algorithm are needed based on those results.

Validated coding algorithms provide quality, reliable definitions for diseases, comorbidities and clinical endpoints, and when well defined and able to be referenced, they strengthen the quality, value, credibility, and replicability of studies. They produce better study results compared to those that may be using imprecise definitions, an absolute necessity in the future for studies being used for regulatory and reimbursement agencies. Organizations can provide consistency of definitions across studies by building a library of validated coding algorithms and appropriate definitions that reflect the clinical events being studied. By referencing them in peer-reviewed publications and providing transparency in database studies, the entire research community is served.

For more information, contact Matthew.Reynolds@evidera.com.

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Quality of the End of Life—Utility Values in Advanced Solid Tumours in Technology Appraisals in the UK

Noemi Muszbek, MSc, Senior Research Scientist, Modeling and Simulation;
Agnes Benedict, MSc, MA, Senior Research Scientist, Modeling and Simulation;
Linda Hortobagyi, MSc, Research Associate, Modeling and Simulation

INTRODUCTION

Set up in 1999 in the United Kingdom (UK), the National Institute for Health and Care Excellence (NICE) provides guidance to the National Health Service (NHS), local authorities, healthcare charities, and healthcare professionals on the most effective ways to prevent, diagnose, and treat disease and ill health, while offering the best value for money and reducing inequalities and variation.[1] These guidances incorporate the technology appraisals that assess the clinical and cost-effectiveness of health technologies according to a rigorous methodological guideline.[2] NICE guidance is mandatory for healthcare providers within the UK and often serves as an example for health technology assessment (HTA) agencies worldwide.

In the development of these guidances, manufacturer submissions are requested to demonstrate the clinical and cost-effectiveness of the healthcare technology, and, together with other stakeholder submissions, are reviewed by the Evidence Review Group (ERG) assigned to that appraisal; in the case of multiple technology appraisals (MTA), a new cost-effectiveness model is developed by the ERG. The decision in recommending the technology is reached by the Review Committee based on the submitted evidence and its assessment according to the process guidelines.[3,4]

In recent years, the evaluation of cancer treatments has represented a large proportion (approximately 30%) of technology appraisals. This is due to the decision of the Department of Health at the end of 2007 to refer "all new cancer drugs and significant new licensed indications" to NICE, preferably in parallel with licensing, if "there is a sufficient patient population and evidence base on which to carry out an appraisal and that there is not a more appropriate alternative mechanism for appraisal."[5] At the same time, the assessment of cancer treatments and the decision rules applicable for the assessment of end-of-life treatments have been in the centre of debates resulting in the establishment of the "end-of-life criteria" and in the setup of the Cancer Drugs Fund. The establishment of the end-of-life criteria in 2009 allows the differential treatment of technologies aiming to extend life in patients with short life expectancy, and those that are licensed for small numbers of patients with incurable illnesses, by placing a higher value at the end of life, and, as a result, allowing for the use of a higher cost-effectiveness threshold.[6] The Cancer Drugs Fund was set up in 2011 for the reimbursement of cancer drugs that were not recommended by NICE.

These developments highlight the importance of discussions and research in the key aspects of technology appraisals of cancer treatments, such as the evaluation of quality of life through established, preference-based generic instruments resulting in utility values. In addition, issues regarding the methods and the face validity of the utility values have received more emphasis in the recent appraisals, for example, that some of the utility values measured in clinical trials in oncology patients are too similar to that of the general public.

Previous research highlighted the potential issues with the use of utility values in the cost-effectiveness studies in oncology and the application of the NICE reference case in the technology appraisals, as described in the NICE methodological guideline.[7–10] A review by Tosh *et al.*[10] examined the utility values in the NICE technology assessments up to 2008, comparing the methodology to the 2004 NICE

reference case. This review identified multiple issues and a large scope for improvement. A more recent review of NICE technology appraisals from the perspective of mapping found poor reporting of mapping methods and a falling proportion of appraisals using mapping.[11]

The aim of this study was to assess the use and elicitation of utility data in the current NICE technology appraisals of advanced oncology treatments in light of the current guidelines. Extrapolation methods will be assessed in an upcoming issue of *The Evidence Forum.*

GUIDELINES FOR UTILITIES AND EXTRAPOLATION

Published in 2013, the current NICE methodological guideline is similar to the previous one in terms of the reference case for utility data *(see Table 1).* The preferred method for measurement of quality of life is still the EuroQol-5D (EQ-5D) questionnaire, with the new version offering five levels in each dimension also mentioned in the new guidelines, although these guidelines do not detail the situations when EQ-5D is not available.

METHODS

Literature Review

A review was conducted to identify all completed NICE technology appraisals for the treatment of advanced solid tumours issued between 2011 and August 2013. Solid tumours were defined as tumours not containing cysts or liquid area.[13]

Data Extraction

Final appraisal documentations, ERG reports, and, where available, manufacturer submissions were reviewed, and the following data were extracted and reviewed.

NICE REFERENCE CASE FOR UTILITIES [2,12]

	2008 NICE reference case	*2013 NICE reference case*
Preferred method of measurement	EQ-5D When EQ-5D data are not available: • Mapping to EQ-5D values • Direct valuation of descriptions of health states using time trade-off	EQ-5D or EQ-5D-5L When EQ-5D data are not available: • Mapping to EQ-5D values If EQ-5D is proven to be inappropriate (e.g., lacks responsiveness & does poorly on tests), then alternative health-related quality of life (HRQoL) measures may be used if its validity is proven. Differences between EQ-5D and the alternative must be shown.
Preferred method of measurement for children	Standardised and validated preference-based measures of HRQoL for use in children, e.g., Health Utility Index 2 (HUI 2)	Standardised and validated preference-based measures of HRQoL for use in children
Measured by	Patients (and carers when impact of treatment on carers' health is important) When not possible, data need to be obtained from carer in preference to health care professionals.	Patients When not possible, data need to be obtained from carer in preference to health care professionals.
Adjustments to values	Not mentioned	Can be made if required (e.g., age, comorbidities)
Preferred source of values	No preference stated If from literature, it needs to be systematic and transparent.	Clinical trial If not available, systematic, transparent literature review.
Valuation of preferences	General public A representative sample of the UK population	General public A representative sample of the UK population
Method of preference elicitation	Choice-based method	Choice-based method

table 1

- Disease area
- Comparators
- ERG
- Issue time of the guidance
- Methods of utility elicitation
- Source of data
- Utility values used in the base case and in sensitivity analyses (both those submitted by manufacturers and the final versions accepted by the Review Committee)
- Criticisms and overall conclusions of the ERG and the Committee
- Final decision of the committee regarding the drugs appraised

Following the most common disease pathway for solid tumours, utility values were extracted for pre-progression (or stable disease) and post-progression health states and were organised into pre- and post-progression pairs. The methods of utility estimation have been compared against the NICE reference case from the 2008 and 2013 NICE guidance[2,12] *(see Table 1).* Data extracted by one reviewer was checked by an additional reviewer.

RESULTS

Twenty-one technology appraisals were identified, 2 of which were terminated and 19 were extracted. There were 17 single technology appraisals and 2 MTAs. The indications where utility data were available were breast cancer, renal cell carcinoma, ovarian cancer, lung cancer, metastatic colorectal cancer, prostate cancer, melanoma, and urothelial tract carcinoma.

All technology appraisals included cost-utility models looking at patients passing through distinct health states (Markov models). These health states included, among others:

- Stable or pre-progression health state defined mostly by the progression-free survival (PFS) curve
- Post-progression or progressed health state
- Death defined by overall survival (OS)

UTILITIES

In the 19 technology appraisals, there were 32 sets of complete, base case, pre- and post-progression utilities reported. Two assessments (TA255, TA259) either did not report or reported only partial utility data. One MTA did not have the manufacturer submission for one of the comparisons.

The mean utility was 0.747 (standard deviation [SD]: 0.06, range: 0.65–0.87) and 0.55 (SD: 0.11, range: 0.25–0.79) for pre- and post-progression, respectively. Among the pre-progression utilities, the majority of utility values were used for patients ages 55–64 (83%); however, the utility values were equivalent to the values of the general UK population ages 75 and older *(see Table 2).* The results were similar for the utility values post-progression, with a slightly higher age.

Only 28% of utility values followed the preferred method of eliciting quality of life in the reference case presented in both the 2008 and 2013 guidelines, and were collected with the help of the EQ-5D questionnaire *(see Table 3).* More than half of the utilities were elicited using direct valuation. Among these, standard gamble was the most common

DISTRIBUTION OF UTILITY VALUES—According to age groups in the appraisal and age group equivalent in the general population

	Distribution of utility values according to the median/mean* age in the trials used as primary source of efficacy data		Proportion of utility values matching the age specific utilities in the general population**	
Age	*Pre-progression*	*Post-progression*	*Pre-progression*	*Post-progression*
75+	0.00%	0.00%	82.54%	96.92%
65-74	0.00%	3.57%	1.59%	3.08%
55-64	85.19%	82.14%	11.11%	0.00%
45-54	14.81%	14.29%	4.76%	0.00%
Below 44	0.00%	0.00%	0.00%	0.00%

**If reported, the median age was used in the analyses. In the absence of median age, the mean age was extracted from the trials, which was used as a proxy for the median age of the patient cohort in the model.*

***Source of values for the different age groups was Kind et al. 1999.[14]*

table 2

METHOD OF UTILITY ELICITATION				
	Proportion of pre-progression utilities		Proportion of post-progression utilities	
	All utilities	*Utilities accepted by Committee*	*All utilities*	*Utilities accepted by Committee*
Indirect valuation	41.38%	43.33%	37.93%	40.00%
EQ-5D	29.31%	26.67%	27.59%	26.67%
HUI	10.34%	13.33%	10.34%	13.33%
Other	1.72%	3.33%	0.00%	0.00%
Direct valuation	58.62%	56.67%	62.07%	60.00%
SG	50.00%	53.33%	58.62%	56.67%
TTO	8.62%	3.33%	3.45%	3.33%
Other	0.00%	0.00%	0.00%	0.00%
Mapping	17.24%	10.00%	5.17%	6.67%

***Abbreviations**: EQ-5D=EuroQol-5 Dimensions; HUI=Health Utilities Index; SG=standard gamble; TTO=Time Trade-off*

table 3

method (54.31%). The majority of these direct preferences were elicited from the general population as per NICE reference case *(see Figure 1).* The methods used for the elicitation of values were similar for utility values submitted by the manufacturers and the ones used by the ERG and also accepted by the Committee. Mapping, however, was more common in the manufacturer submissions than among the values recommended by the ERG and the Committee *(see Table 3).*

The overwhelming majority of utility values came from the literature (60.3% and 80.7% pre- and post-progression, respectively), including previous technology appraisals. More pre-progression utilities were available from trials compared to post-progression values (37.9% and 19.3% pre- and post-progression, respectively).

Although pre- and post-progression utilities overlapped, there seems to be a trend for post-progression values being lower. Utility values from the manufacturer submissions and recommended by the ERGs or Committees are similar, with the latter slightly lower *(see Figure 2).* Values were usually held highly uncertain, and in 75% of cases a univariate sensitivity analysis was conducted.

MOST COMMON CRITICISM FROM THE ERG OR THE COMMITTEE

Utility values were criticized by both ERGs and the Review Committee in almost all cases. The most common criticisms were regarding the methodology and the face validity. Criticism regarding the methodology included the following:

- In many cases, the method of data collection was described in insufficient detail, leading to increased uncertainty.
- Utilities were not collected in the clinical trials.
- Utility data collected in the trials was not representative of the patients throughout the progression of the disease.
- Utilities in the model were not derived according to the NICE reference case.
- Disutilities for adverse events were not incorporated into the model.
- Literature review of utility values was not systematic.

Criticism regarding face validity centred on 1) doubts if the values were representative of the patient population evaluated (e.g., in terms of age, country, health status; and/or 2) the values not reflecting the impression and experience of the disease or the course of the disease in 42% of the technology appraisals. Values were compared to that of the general population and were expected to be significantly lower. Differences between pre- and post-progression utilities were also assessed and criticized if minor.

The expectations also varied according to the particular ERG. For example, in breast cancer, the commonly used source of data from Lloyd *et al.*[15] was accepted or required by some of the ERGs, yet was criticized by another ERG for not being in line with the NICE reference case.

DISCUSSION

In light of the recent publications on the use of utility values in oncology, a review of the latest NICE technology appraisals of advanced cancer treatments was conducted to assess the use and elicitation of utility data. The results show that in the majority of cases the requirements of the NICE reference case were not met. EQ-5D was used in only 27% of cases, and, depending on progression status, clinical trials were the main source of data in only 19%–38% of cases. Although often criticized for lack of face validity, on average the difference between pre- and post-progression utilities was 0.197, and on average the values were lower than that of the general population in the same age group.

Despite the criticism of the utility values from the manufacturer submissions, they were very similar to the final values recommended by ERGs and accepted by the Committee, suggesting a lack of better alternatives. This was especially important for the post-progression utilities, where even the values elicited according to the NICE reference case raised concerns regarding face validity. Due to these concerns, the values elicited according to the NICE reference case were occasionally substituted with other types of utilities, such as with directly elicited values.

Thus, despite the new NICE guidance reinforcing the requirements for utility values, the methods used still vary, as in the previous finding by Tosh *et al.*[10] Meanwhile, the use of the EQ-5D is less than half (28%–29%) in these recent oncology appraisals

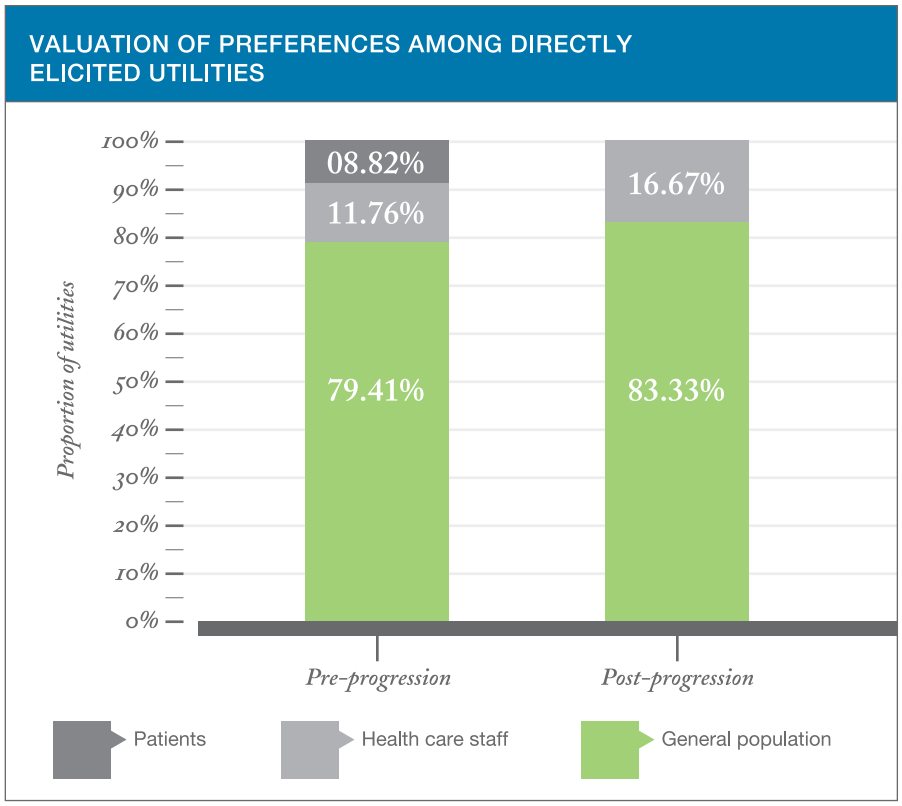

figure 1

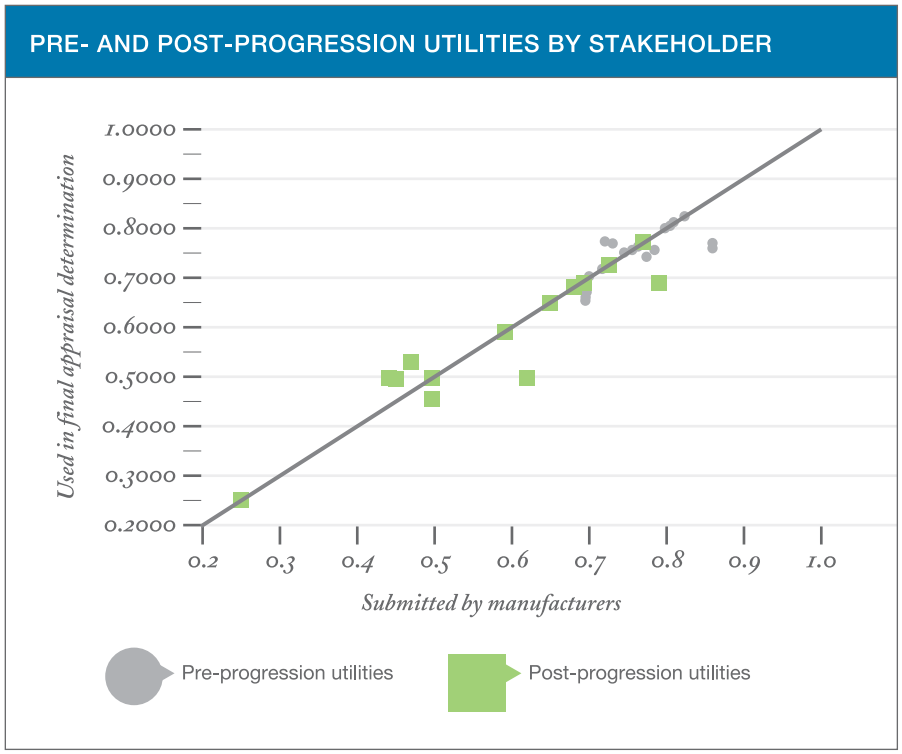

figure 2

UNCERTAINTY AROUND THE UTILITY VALUES CONTRIBUTES TO THE UNCERTAINTY AROUND THE INCREMENTAL COST-EFFECTIVENESS RATIO IN ONCOLOGY; THIS NECESSARILY FOCUSES THE ATTENTION ON THE METHODOLOGIES AND FACE VALIDITY OF THESE UTILITY INPUTS.

compared to all therapeutic areas assessed prior to 2009 (64%). This might be reflective of the concerns expressed in recent publications about the use of EQ-5D in cancer.

In a 2011 review, Garau *et al.*[7] assessed utility valuation in oncology, with special emphasis on EQ-5D in three methodological areas (the description of health states, the valuation of health states, and whose values are taken into account) and identified various potential flaws. Due to the five dimensions and three levels leading to limited number of unique health states (243), the EQ-5D lacks sensitivity. There is work ongoing exploring both the potential increase of the number of dimensions[11] and increasing the number of levels to five.[16] This, however, poses additional questions with regards to complexity and the need to evaluate more health states. Mapping from cancer-specific instruments, such as the Functional Assessment of Cancer Therapy (FACT) or the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30), have been explored to overcome this limitation.[8,17] However, mapping has its own issues.[11]

In the valuation of the health states determined by EQ-5D, one of the key issues is the assumption of constant proportional trade-off with the time trade-off method, i.e., the proportion of life expectancy traded off for an improvement of quality of life is constant for the individuals, independent of the length of life expectancy. This assumption may be violated when life expectancy is very short, as among patients with advanced cancer.[14] There is also the issue of the potential difference between the valuation of the general public and the patients themselves. The trade-off, between giving sufficient information to the general public to allow them to assess the health state without bias or misunderstanding and the provision of too much detail that can elicit misconceptions, is an important issue.

Of course, utility values for advanced oncology indications collected in clinical trials have their own set of issues. The timing of the assessment can be crucial with regards to toxicities.[9] Patients are not followed up until death regularly; data collection often stops soon after treatment discontinuation or progression. If they are followed-up, there is a very large attrition rate in quality of life measures even when other measures are available. Thus values that represent the quality of life of patients toward the end of life are usually scarce.

The use of values from trials in classic, three health state Markov models also assumes that patient quality of life changes after radiologic progression. This however may not be the case in indications where the symptomatic progression happens at a much later time point or where quality of life changes with the discontinuation or switching of treatments, rather than progression.

Although the results found in the review seem reflective of the methodological challenges debated in the literature, this study has various limitations. Utility values or method of elicitation were not always available publicly due to reporting or confidentiality (commercial or academic), and these missing data might bias the results. The average age of patients in the modeled cohorts was not available in most cases. Thus the median or mean age of patients in the clinical trials reported as the primary source of the efficacy data were used as a proxy. However, this might not accurately reflect the patient population used in the base case of the model. Thus the interpretation of these results is not straightforward. In addition, the precise effect of these uncertainties on the decisions (i.e., the link between the different aspects of the utilities and their acceptance by the Committee) has not been explored.

CONCLUSIONS

Uncertainty around the utility values contributes to the uncertainty around the incremental cost-effectiveness ratio in oncology; this necessarily focuses the attention on the methodologies and face validity of these utility inputs. Although the 2013 NICE methods guidance reinforced the need for utilities measured in clinical trials with the help of the EQ-5D questionnaire from patients, methods of elicitation still often do not conform to the NICE reference case. In the post-progression health state, even values elicited according to the NICE reference case have raised various concerns. These concerns regarding the source, measurement, and interpretation of utility values reflect the recent debates regarding the potential challenges of using EQ-5D values in oncology and stress the importance of methodological development. Also, although the assessment of utilities in advanced oncology indications is crucial in terms of cost-effectiveness, in many cases it is not incorporated or is not incorporated *appropriately* in the design of the Phase 3 clinical trials.

Acknowledgements

The authors would like to thank Rebecca Baggaley, Chantelle Browne, Corina Chalkiadaki, David Gabriel, Panagiotis Orfanos, Zachary Smith, Dylan Trundell, and Meng Wang at Evidera for their help in the data extraction.

For more information, please contact Noemi.Muszbek@evidera.com, Agnes.Benedict@evidera.com or Linda.Hortobagyi@evidera.com.

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Virtual Population Simulation as a Source of Expected Event Rates

Badri Rengarajan, MD, Vice President, Medical Affairs and Senior Principal Consultant;
Kenny Shum, PhD, Scientist, Modeling and Simulation

Estimating the number of patients needed for a clinical study (i.e., sample size estimation) is critical to formulating a statistically robust trial design that avoids generating inconclusive results. The literature contains several examples of trials that failed to generate conclusive results due to insufficient sample size, with reasons varying from poor sample size estimation, poor enrollment or patient dropout.[1,2] Sample size also has major implications on the cost and timing of a clinical trial.

A key determinant to sample size estimation is the expected rate of events in the trial population. Uncertainty about expected rates in the target population poses a challenge for estimating sample size. While clinical trialists can use observed rates drawn from prior relevant studies or risk engines to inform expected rates, such as those for cardiovascular events (e.g., Framingham, ARIC, Dundee, SCORE), these sources can vary substantially in their estimates. Additionally, comparing results across these sources is difficult because the source populations on which they are based can vary by demographic characteristics, geography, healthcare system, clinical history, and severity of disease. For instance, the frequently used Framingham Risk Score, which estimates the 10-year risk of developing coronary heart disease and is useful in informing physicians and patients about cardiovascular risk, has become outdated over time as clinical guidelines and healthcare practice patterns have changed.

Virtual population simulation can help overcome some of these limitations. Simulation allows one to play out the lives of thousands of virtual patients as they accumulate disease burden; to include current and evolving clinical practice; and to forecast the expected rate and pattern of event rates over several years (e.g., myocardial infarction [MI], major adverse cardiac events [MACE], renal progression) for a given population. A theoretically unlimited number of scenarios with different populations, treatment guidelines, and patient behaviors (e.g., medication non-compliance) can be run simultaneously—with results available today. The use of virtual population simulation allows researchers to examine how inclusion/exclusion criteria affect the characteristics of the baseline population and the size of the eligible population.

CASE STUDY: FORECASTING MACE RATES FOR PLANNING A CARDIOVASCULAR (CV) OUTCOMES TRIAL

The anti-obesity space has historically been a "Bermuda Triangle" filled with failed or withdrawn drug candidates. One drug was withdrawn from the market due to heart valve damage; another was withdrawn due to CV risk; and yet another did not receive U.S. Food and Drug Administration (FDA) approval due to suicide risk. However, recently there have been successes. Two drugs were approved in 2013 but only after overcoming birth defect and cancer risk issues, respectively.

A biopharmaceutical company is developing a drug for obesity and weight management which is a combination of two approved and marketed drugs, one used for smoking cessation and the other for alcohol dependence. Based on trial data showing weight loss with the new drug, an FDA advisory committee recommended approval with a **post-approval** commitment to study CV safety risks. However, in early 2011, the FDA issued a Complete Response Letter stipulating the need for a **pre-approval** CV outcomes trial as well.

After some negotiation, the company and the FDA eventually arrived at a "reasonable and feasible" path forward that could enable resubmission of the New Drug Application (NDA). The FDA had several stipulations on trial design, including:

- Background rate of 1.0–1.5% risk of major CV event (annual)
- 95% confidence interval (CI) to exclude a hazard ratio (HR) of 2.0 and 1.4 at interim analysis and final analysis

As a result, a trial design was needed that was acceptable to the FDA and resource-efficient with sufficient MACE events, optimal study enrollment and duration, and clear interpretation. For background CV event rate determination, the company used

Phase 3 data and published CV risk engines to estimate 10-year risk.[3] While results were encouraging, the risk engines had limitations, including:

- Lack of consistent patient population across engines
- Current standard of care not uniformly implemented across engines
- Inconsistent endpoints available across engines (e.g., MI not available in all engines)

A decision was made to pursue simulation, specifically the exploration of the contributions of different inclusion/exclusion (I/E) criteria to MACE event rates. Several population subgroups were identified based on variations of I/E criteria, e.g., High-risk CV with:

- Age >50, BMI >27
- Age >50, BMI >30
- Age >50, BMI >30 + HTN (hypertension)
- Age >50, BMI >30 + HTN + DM (diabetes mellitus)

Combinations were also based on: age, sex, body mass index (BMI), weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting plasma glucose (FPG), HbA1c, high-density lipoprotein (HDL), low-density lipoprotein (LDL), smoking status, and other parameters.

Patients were then drawn at random from the virtual population, and those virtual patients meeting I/E criteria variations were recruited into the simulation. Event rates (MACE and MACE components—MI, stroke, cardiovascular disease [CVD] death) were estimated annually for each I/E criteria scenario over a 10-year period. Projected MACE rates of I/E criteria variations enabled the company to understand expected rates and to sculpt the trial population.

The simulation data were shared with the FDA after the Complete Response Letter was received and during negotiations with the FDA on securing clearance for its CV study protocol. In February 2012, the FDA cleared the company's study protocol.

In conclusion, which methods or tools will work best to address specific study needs depends on the availability and reliability of expected event rate data and applicability of risk scores to the population of interest. The clinical trialist now has more options, however, to generate or refine estimations—including virtual population simulation.

For more information, please contact Badri.Rengarajan@evidera.com or Kenny.Shum@evidera.com.

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Upcoming Presentations

DIA EUROMEETING

Mar 25–27, 2014
Vienna, Austria

ORAL PRESENTATION

Using Virtual Population Simulation to Improve Protocol Design and Amendment Management

Badri Rengarajan, MD, VP Medical Affairs and Senior Principal Consultant, Evidera

ACC.14 63RD ANNUAL SCIENTIFIC SESSION

Mar 29–31, 2014
Washington, DC, USA

POSTER

Medical Costs Avoided for Prevention of Stroke with Use of NOACs: Estimates for the Real-World

Amin A, **Stokes M,** Makenbaeva D, Wiederkehr D, Gatt E, **Wu N,** Lawrence JH

2014 HMORN

Apr 1–3, 2014
Phoenix, AZ, USA

ORAL PRESENTATIONS

Forecasting Disease Burden and Health Utilization in Uninsured Populations in California Health Insurance Exchange Pricing Regions

Tuan Dinh, PhD, VP, Archimedes Modeling and Analytics, and Sr. Research Scientist, Evidera

Risk Engine Evaluation Software: An Analytics Platform for Individualized Guidelines

Tuan Dinh, PhD, VP, Archimedes Modeling and Analytics, and Sr. Research Scientist, Evidera

AMCP'S 26TH ANNUAL MEETING AND EXPO 2014

Apr 1–4, 2014
Tampa, FL, USA

POSTER

The Epidemiology of Opioid-Acetaminophen Combinations Exposure and Acetaminophen Toxicity in the United States

Blieden M, Paramore LC, Shah D, Ben-Joseph R

AAN AMERICAN ACADEMY OF NEUROLOGY 66TH ANNUAL MEETING

Apr 26–May 3, 2014
Philadelphia, PA, USA

POSTERS

Peginterferon Beta-1a Treatment Reduces the Impact of Multiple Sclerosis Relapse and Disability Progression on Health-Related Quality of Life: Results from the ADVANCE Trial

Kinter E, **Guo S, Altincatal A, Proskorovsky I,** Phillips G, Sperling B

Psychometric Properties of the MSIS-29 and Factors Predicting Score Changes in Clinical Trials: An Analysis of Data from the SELECT Study

Phillips G, Castelli-Haley J, **Guo S, Proskorovsky I,** Elkins J

PRO/COA SUMMIT

May 6–7, 2014
Philadelphia, PA, USA

SESSION SPEAKER

Psychometrics—Rasch Item Response Theory vs. Classical Test Theory

Kathleen W. Wyrwich, PhD, Sr. Research Leader, Outcomes Research, Evidera; Joseph C. Cappelleri, PhD, Sr. Director, Biostatistics, Pfizer

APA ANNUAL MEETING

May 3–7, 2014
New York, NY, USA

POSTER

The Effect of Lurasidone on Functional Remission Measured by the Sheehan Disability Scale

Hassan M, **Dansie E,** Rajagopalan K, **Wyrwich K,** Loebel A, Pikalov A

BIG DATA IN PHARMA CONFERENCE

May 12–13, 2014
London, UK

WORKSHOP

Designing and Commissioning Studies Using Big Data to Support Drug Development and Marketing

Andrew Cox, PhD, Sr. Research Associate; **Rob Thwaites, MCom,** Vice President Health Economics; **Radek Wasiak, PhD,** Sr. Research Scientist, Health Economics and Epidemiology, Evidera

ATS 2014 INTERNATIONAL CONFERENCE

May 16–21, 2014
San Diego, CA, USA

POSTERS

Evaluation of the Psychometric Properties of the Nighttime Symptoms of COPD Instrument (NiSCI)

Mocarski M, **Hareendran A,** Jen MH, **Zaiser E,** Make BJ

Study Design of a 1-year Prospective, Observational Registry of Treatment Patterns and Outcomes for Patients with Chronic Obstructive Pulmonary Disease (iSTEP)

Massaro S, Zhang J, Williams J, Hakanson D, Arcona S, Turner SJ, **Wilcox TK,** Desrosiers MP, Payne K

COOPERATIVE MEETING OF THE CMSC AND ACTRIMS

May 28–31, 2014
Dallas, TX, USA

POSTER

Understanding Drivers of Employment Change in a Multiple Sclerosis (MS) Population

Coyne K, Currie B, Landrian A, Boscoe A, Wandstrat T

EULAR 2014

Jun 11–14, 2014
Paris, France

POSTER

Evaluation of Dimensionality and Sensitivity in Physical Functioning Construct When Combining the Health Assessment Questionnaire with the SF-36 Health Survey Physical Functioning Scale

Lin CY, al Sawah S, Zhu B, **Wyrwich K, Kawata A,** Zhang X, Naegeli A

DIA 2014 50TH ANNUAL MEETING

Jun 15–19, 2014
San Diego, CA, USA

ORAL PRESENTATIONS

Bolstering Development Programs in Rare Diseases: Simulating Clinical Trials with a Virtual Patient Population

Badri Rengarajan, MD, VP Medical Affairs and Senior Principal Consultant, Evidera

Using Virtual Population Simulation to Forecast Likely Study Outcomes as a Trial is Enrolling

Badri Rengarajan, MD, VP Medical Affairs and Senior Principal Consultant, Evidera

Using Virtual Population Simulation to Generate Insights on Drug Performance in Special Populations

Badri Rengarajan, MD, VP Medical Affairs and Senior Principal Consultant, Evidera

EU WONCA

July 2–5, 2014
Lisbon, Portugal

POSTER

The Patient Impact of Opioid-Induced Constipation (OIC) on Pain Management and GI Symptoms

Datto C, LoCasale R, **Wilson H, Coyne K,** Tack J

JSM JOINT STATISTICAL MEETINGS

Aug 2–7, 2014
Boston, MA, USA

SESSION SPEAKER

Big Data Tool for Estimating Baseline Event Rates in Clinical Trials

Roshan Shah, Manager, Client Services, Evidera

Recent Presentations

ASCPT 2014 ANNUAL MEETING

Mar 18–22, 2014
Atlanta, GA, USA

SYMPOSIUM

New Applications of Quantitative Approaches in a Changing Health Care Environment—Incorporating Effectiveness and Cost in Our Models

SPEAKERS: Sebastian Schneeweiss, MD, ScD, Harvard Medical School; **J. Jaime Caro, MD,** Evidera/McGill Univ.; Brian P. Smith, PhD, Amgen; Rebecca Boyd, PhD, Pfizer

AHA EPI/NPAM 2014

Mar 18–21, 2014
San Francisco, CA, USA

POSTERS

Association between Chronic Kidney Disease, Blood Pressure, HbA1c, and Body Mass Index with Healthcare Resource Utilization and Costs in Type 2 Diabetes Mellitus Patients

Chuang CC, Lee E, **Yang E,** Ghosh S, **Tawah A,** Chen SY

Healthcare Resource Utilization and Associated Costs in Type 2 Diabetes Mellitus Patients with Uncontrolled Glycemic Level or Blood Pressure

Chuang CC, Lee E, Bhurke S, Ghosh S, **Tawah A,** Chen SY

38TH HAWAII DERMATOLOGY SEMINAR

Feb 16–21, 2014
Big Island, HI, USA

POSTER

Racial Differences in Clinical Characteristics, Perceptions, and Behaviors among Adult Females with Acne Vulgaris

Rodriguez DA, Rendon MI, Burk C, **Kawata AK,** Degboe A, **Wilcox TK,** Daniels SR, Roberts WE

ePHARMA

Feb 10–12, 2014
New York, NY, USA

ISSUE PANEL

The Massive Changes Impacting U.S. Healthcare and the Actions Pharma Must Take to Adapt to this New Healthcare Future

Badri Rengarajan, MD, VP Medical Affairs and Senior Principal Consultant, Evidera

HARVARD SCHOOL OF PUBLIC HEALTH—2014 GLOBAL HEALTH AND POPULATION BROWN BAG SERIES

Feb 6, 2014
Cambridge, MA, USA

ORAL PRESENTATION

QALYphilia: A Cure?

J. Jaime Caro, MDCM, FRCPC, FACP, Chief Scientist, Evidera

ODAC ORLANDO DERMATOLOGY AESTHETIC AND CLINICAL CONFERENCE

Jan 17–20, 2014
Orlando, FL, USA

POSTERS

Impact of Adult Female Acne Characteristics on Patterns of Health Care Resource Utilization

Tanghetti E, Burk C, **Kawata A,** Daniels S, **Wilcox T,** Baldwin H

Impact of Adult Female Acne Characteristics on Patterns of Health Care Resource Utilization: Predictors of Medication Use

Baldwin H, **Kawata A,** Daniels S, **Wilcox T,** Burk C, Tanghetti E

ASH 55TH ANNUAL MEETING AND EXPOSITION

Dec 7–10, 2013
New Orleans, LA, USA

ORAL PRESENTATION

Psychometric Evaluation Of Health-Related Quality Of Life Assessments From the ALONG and BLONG Hemophilia Clinical Trials

Wyrwich KW, Auguste P, von Maltzahn R, Yu R, Krishnan S, Dodd N, von Mackensen S

PFF PULMONARY FIBROSIS FOUNDATION SUMMIT

Dec 5, 2013
La Jolla, CA, USA

POSTER

Outcomes and Costs Related to Hospitalizations and Exacerbations among Commercially Insured Patients Newly Diagnosed with Idiopathic Pulmonary Fibrosis

Wu N, Yu Y, **Chuang CC, Wang R, Benjamin N,** Coultas D

ABPI-NIHR CONFERENCE: 360 DEGREES OF HEALTH DATA—HARNESSING BIG DATA FOR BETTER HEALTH

Nov 21, 2013
London, UK

ORAL PRESENTATION

Industry's Data Needs: 2020 Vision

Rob Thwaites, MA, MCom, VP Health Economics, Evidera; Hilary Thomas, MA, Partner and Industry Specialist, KPMG Global Healthcare Center of Excellence

Company News

EVIDERA ACQUIRES ARCHIMEDES, ENHANCING MODELING AND SIMULATION OFFERINGS AND EXPANDING REACH TO CLINICIANS

On January 8, Evidera announced the acquisition of Archimedes, Inc., a San Francisco-based healthcare modeling and simulation company providing consulting services, software products (ARCHeS), and a clinical point-of-care solution (IndiGO). The addition of the Archimedes Model and advanced software and data interface capabilities enhances Evidera's modeling and simulation offerings and opens new territory in providing evidence directly to healthcare providers and patients.

THE ARCHIMEDES MODEL

The Archimedes Model is a large-scale, clinically realistic simulation model of physiology, disease outcomes, and healthcare system interactions. It was initially developed in 1993 by David Eddy, MD, PhD, and Len Schlessinger, PhD, and was built to represent physiological, clinical, and administrative events as they occur in reality.

The model enables the user to play out the lives of thousands of virtual patients, each of whom is represented as a series of trajectories of correlated risk factors, such as clinical biomarkers, medical history, and medication use. The model can forecast the clinical and economic outcomes of care interventions. The model includes customizable populations that can be matched to real populations; multiple conditions (cardiovascular diseases, diabetes, COPD, and lung, breast, colorectal, and bladder cancers); healthcare delivery systems; patient and physician behaviors; and customizable interventions, tests, and treatments. Running on a distributed computing network enables the model to rapidly calculate the effects of interventions on clinical outcomes, utilization, quality of life, and financial costs. The Archimedes Model has been validated against several landmark clinical trials and epidemiological databases and surveys.

Many organizations have used the model to help answer a wide variety of questions related to clinical trial design, health economics and outcomes research, portfolio prioritization, policy setting, and market access. The list of clients and collaborators includes academic and research institutions, voluntary health organizations, national and international governmental organizations, and major pharmaceutical companies.

ARCHeS

With the acquisition of Archimedes, Evidera is now able to offer ARCHeS, a suite of online healthcare simulation and analytics tools using the Archimedes Model simulation platform. Users can create and run their own simulations as well as analyze and compare real-world and simulated datasets using analysis and reporting tools. The development of ARCHeS was funded by a multi-million dollar grant from the Robert Wood Johnson Foundation which sought to ensure that the Archimedes Model would be widely accessible to public sector decision makers.

MODELING TEAM

With the addition of over two dozen scientists, software team members, and a medical director from Archimedes, Evidera now has the largest modeling team in the healthcare modeling field. Some of the key modeling leaders who have joined Evidera's team through this acquisition are listed below.

- Tuan Dinh, PhD, provides strategic and tactical leadership to analytics and modeling activities. His areas of expertise include health economics and outcomes research, risk assessment and management, cost-effectiveness analysis, payer/provider analytics, clinical decision support systems, clinical trial design, and big data applications. His recent work includes prevention, screening and treatment of cancers, diabetes and cardiovascular diseases, genomic and genetic testing, mental health, and medication adherence.
- Paul Jasper brings over 30 years of software development expertise to Evidera. In his seven years at Archimedes, he introduced new technologies that led to major performance improvements, easier model development, and flexible healthcare protocol modeling. He is the senior architect of the software development team that works collaboratively with scientists to extend the Archimedes Model, add new features to ARCHeS, and improve the performance and reliability of the products.
- Badri Rengarajan, MD, provides clinical input to modeling and analytics projects, leads consulting engagements, and builds relationships with clinical research leaders. He also provides clinical support to the IndiGO clinical decision support

program. Badri's areas of expertise include clinical trial design, drug and diagnostic development, health analytics, and strategy. Badri has over 15 years of healthcare industry experience including roles in product development strategy and new product planning, regulatory affairs, market research, and business development.

- Andy Schuetz, PhD, leads the development of the ARCHeS suite of software products. He is passionate about combining large-scale computing and analytics with web-based products to tackle the challenges faced by healthcare and life sciences today. Andy has 9 years experience in the healthcare and medical device spaces. His publications have focused on comparative effectiveness and cost -effectiveness analyses for the management of diabetes and cardiovascular disease.

IndiGO

IndiGO expands Evidera's offerings reach to the clinical point-of-care through deployment to accountable care organizations (ACOs), integrated delivery networks, independent practice associations, and patient-centered medical homes. The software enables the combination of real-world healthcare data and simulation to create compelling and actionable evidence used in individual healthcare decision making. The IndiGO offering enables healthcare providers and patients to make informed decisions about treatments and preventive care.

IndiGO TEAM

Key leaders for the IndiGO offering include:

- Josh Adler leads the commercialization of IndiGO (Individualized Guidelines and Outcomes), an application of the Archimedes Model. Josh is responsible for overall business leadership of IndiGO, including strategy, sales, and business development activities. Josh has over 25 years of experience, primarily in venture capital-supported health services companies.
- Don Morris, PhD, leads the development of IndiGO and other products based on the individualized risk prediction and decision support methods he created in 2007. He is also responsible for research into new modeling technologies, quality control, and intellectual property development. Don has over 17 years of experience in bioinformatics and technology development.
- Brian Zuzga, MEng, manages the development of the IndiGO product, which provides individualized recommendations at the point of care, population management capabilities, and consumer applications. Brian has 19 years experience in the software and web application space and is a named inventor on six patents. Brian has experience working both in larger software organizations, like Oracle, CA, and BEA, and small, dynamic startups, like PointCast, Wily Technology, and ChemConnect.

DR. JAIME CARO TO TEACH PHARMACOECONOMICS COURSE AT MCGILL UNIVERSITY

The assessment of pharmaceuticals has expanded beyond efficacy and safety to cover their economic implications and other consequences. This course provides a detailed introduction to the key concepts of this field. Study types and corresponding decision rules are examined. A detailed example is used to highlight the development, population, and advantages of simulation modeling, as well as analysis of results.

Dates: May 26–29, 2014
Instructor: **Dr. Jaime Caro,** Chief Scientist at Evidera and Adjunct Professor of Medicine, Adjunct Professor of Epidemiology and Biostatistics at McGill University.

For more information, visit www.mcgill.ca/epi-biostat-occh/summer/coursestimetables.

EXACT HAS A NEW WEBSITE!

The EXACT (The **EXA**cerbations of **C**hronic Pulmonary Disease **T**ool) has a new website, redesigned to provide easy access to information related to the EXACT and E-RS. The EXACT was developed under the EXACT-PRO Initiative, a multi-year, multi-sponsor project that led to the first FDA qualified patient-reported outcome (PRO) measure for use in drug development trials.

Please visit the new website to learn more about the EXACT and E-RS. http://www.exactproinitiative.com.

Company News

EVIDERA WELCOMES NEW SENIOR STAFF

David Alderson, MBA
European Practice Lead,
Payer Research and Strategy

David is responsible for leading the European based payer research team and supporting clients with their market access needs. Most recently, David spent over four years at GfK Bridgehead as Vice President—Europe, where he was responsible for one of the market access consulting teams (with a particular focus on small to medium pharma/biotech companies as well as the MedTech sector). Prior to consulting David worked for NAPP, AstraZeneca/Medimmune, Novartis, and GSK in various global and national roles covering a range of disciplines from marketing to strategic planning and merger integration implementations. David received his MBA from the Cranfield School of Management.

Cheryl Ball
US Practice Area Lead,
Payer Research and Strategy

Cheryl has over 15 years of experience in pharmaceutical commercial strategy focusing on new product planning, market access and franchise growth, with specific expertise in aligning scientific, clinical, patient and health economics perspectives to define a clear value story for new products. Prior to joining Evidera, Cheryl was Director, Strategy and External Insights for the New Opportunities iMed at AstraZeneca, and she also has worked for Quintiles and Decision Resources Consulting where she led projects focused on new product planning and business development, including commercial assessment, market access strategy, value propositions and launch strategies. Cheryl received her BSFS in international economics/finance and commerce from Georgetown University.

Randall Bender, PhD
Senior Psychometric Statistician,
Outcomes Research

Randall's responsibilities include psychometric analyses, including Rasch and IRT, and other latent variable and statistical modeling. Prior to joining Evidera, Randall was a Senior Research Psychometrician at RTI, where he was a resident expert in social science data analysis and scaling/measurement techniques, consulting on statistical and psychometric projects and leading data analysis teams. Randall received his masters and PhD in quantitative psychology from the University of North Carolina at Chapel Hill, followed by postdoctoral study in quantitative psychology at the University of Illinois at Urbana/Champaign.

Find a Career
Make a Difference

Mike Epstein, MSc
Director, Market Access, Complex Access and Pricing Strategy

For over 15 years, Mike has specialized in payer research and strategy development, conducting hundreds of payer interviews, moderating advisory boards, and leading quantitative projects. Mike was formerly the Director of Commercial Strategy for UBC and prior to that was a Senior Project Manager for Abt Biopharma Solutions which was acquired by UBC in May 2010. Mike received an MA in political science, MSc in public policy and BA in political science from the University of Rochester in NY.

Dorota Staniewska, PhD
Psychometric Statistician, Outcomes Research

Dorota's expertise includes item response theory, multidimensionality, nonparametric statistics, scale construction, and sampling and weighting. Prior to joining Evidera, Dorota was a Psychometrician for the Financial Industrial Regulatory Authority (FINRA) where she managed a battery of computer-based financial licensure exams and introduced and extended pretesting to exams resulting in better measurement. Dorota received her PhD in educational measurement from Rutgers University, an MS in statistics from the University of South Carolina and a BA in mathematics from Smith College.

Evidera is seeking highly qualified and motivated researchers to join our expanding international team.

We are looking for innovative researchers with experience in the following areas:

HE modeling and simulation
Patient-reported outcomes
Biostatistics
Epidemiology
Payer research
Market access communication
Systematic literature reviews

Positions are available in the United States, Canada and Europe.

For more information and consideration, please visit our website at www.evidera.com/careers.

Evidera

Evidera

CORPORATE HEADQUARTERS
7101 Wisconsin Avenue, Suite 600
Bethesda, MD 20814

contact Susan Potter Couch
phone +1 301 654 9729
fax +1 301 654 9864
email info@evidera.com

WWW.EVIDERA.COM

The Evidence Forum is an official publication of Evidera, providing evidence, value and insight through evidence-based solutions that enhance patient care and help people live longer, healthier lives.

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