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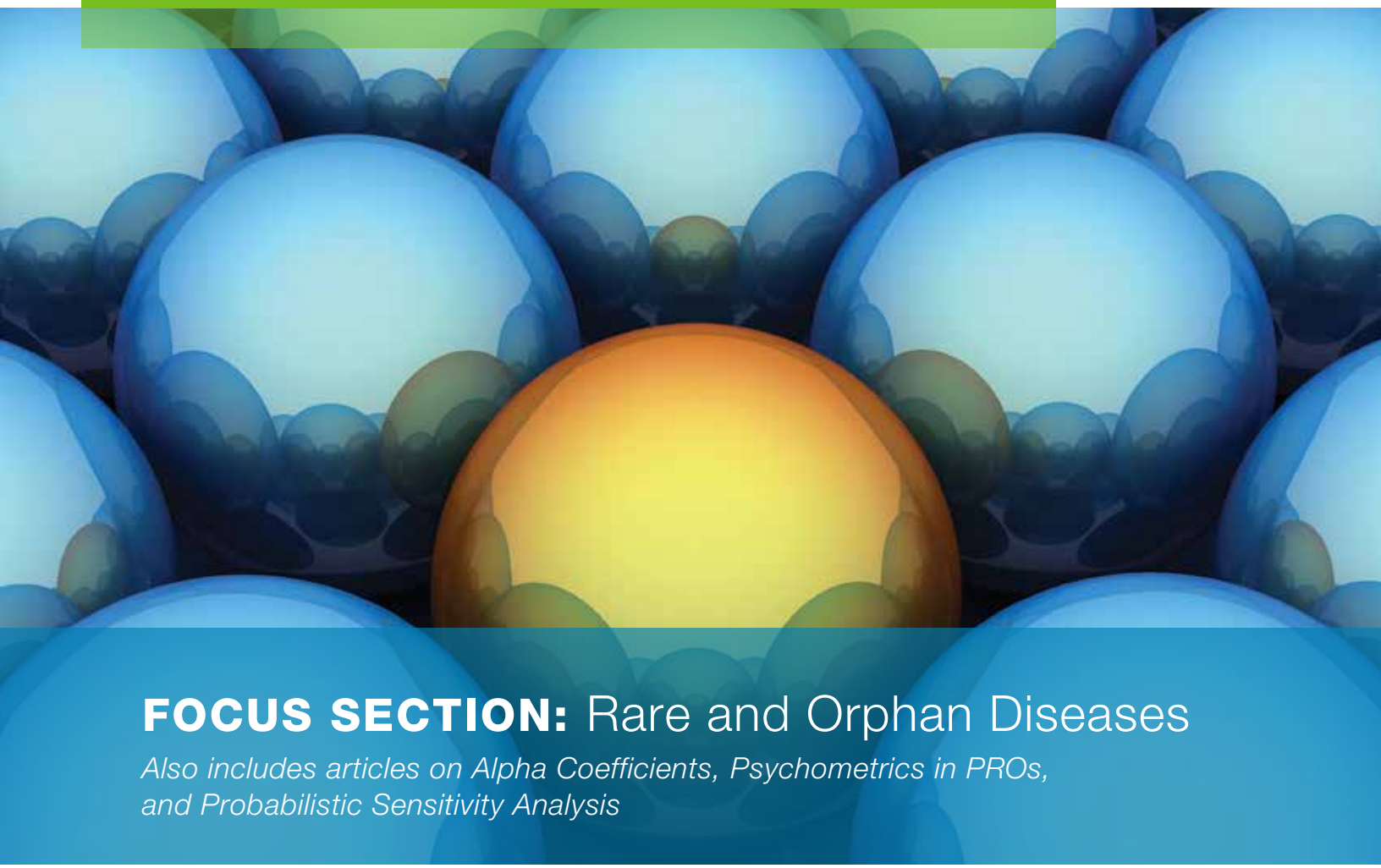

FOCUS SECTION: Rare and Orphan Diseases

Also includes articles on Alpha Coefficients, Psychometrics in PROs, and Probabilistic Sensitivity Analysis

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Help Wanted:
An Emerging Opportunity in Rare Disease Research

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NEW CHALLENGES FOR PATIENTS WITH RARE DISEASES

Patients with rare diseases have played important roles in discovery and translational research programs needed to find cures and treatments. They had to. The causes of their diseases were unknown or too small to attract the attention of researchers and industry. The patients formed advocacy groups, established their missions and set course. They found researchers to search for discoveries, organized research networks for clinical trials and volunteered as human subjects. They established registries and raised funds to support discovery and translational research programs. In the process, they gained knowledge and experience in getting promising treatments from the laboratory into clinical trials and eventually through regulatory review. And, they have been effective; think of ivacaftor (Kalydeco) for cystic fibrosis, alglucosidase alfa (Myozyme) for Pompe disease, and cysteamine ophthalmic solution (Cystaran) for corneal crystals from cystinosis, to name just a few. However, the patients and their patient groups did not do all this alone; they formed partnerships with pharmaceutical manufacturers, medical device makers, academic researchers and commercial research organizations.

These patients are now facing new challenges that research can again help them overcome. Manufacturers and regulators do not always consider outcomes valued by patients, which risks approval denials for products that could have addressed issues important to patients. Clinicians are not always attuned to signs and symptoms of rare diseases, which leaves some people undiagnosed and untreated. Payers are demanding evidence about total cost impacts, patient outcomes, and patient preferences, and not having that information available can lead, in some cases, to decisions against coverage. The types of information needed to address these challenges are not new to the healthcare industry and research community in general, but they are new as now applied to drugs and devices in rare diseases. Rare disease patients can rise to these challenges, but they will need help from organizations with expertise in the research methods needed to design and execute studies to fill in the evidence gaps for manufacturers, regulators, clinicians and payers.

Thus, rare disease patient groups are looking for the right partners — those that understand rare disease patients and their organizations — with the right research programs — those that bring all the support mechanisms needed for patients to fully participate. My objective with this article is to characterize rare disease patients and provide ideas on the elements of programming that would contribute to successful collaborations.

I hasten to add that many rare disease patients wish they had this challenge. The National Institutes of Health (NIH) estimates that there are more than 6,800 rare diseases,[1] and yet there are only about 400 drugs for 450 rare disease indications. While coverage policy problems in particular are actually a sign of success for rare disease research, developing diagnostics and treatments remain the biggest challenge for most of the rare diseases.

THE RIGHT PARTNERS UNDERSTAND RARE DISEASE PATIENTS

I approach any attempt to characterize rare disease patients with trepidation. A dominant characteristic of these patients generally is the variability among them that matches the variability among the general population. I will, however, make a few generalizations that should help researchers understand rare disease patient involvement in research and the frameworks shaping some of their expectations and demands.

Patient advocacy groups are usually the main conduit for patients involved in rare disease research. Hundreds of rare disease patient advocacy groups have formed, and indeed several groups can exist for just one disease. Although research for a cure or treatment is very often their top priority, the people in these groups do not come to them from a primary interest in biomedical research, or even much of an interest in biomedicine at all. They come out of necessity and with urgency because they or someone they know has been stricken with a rare disease. They are people from commerce, government, education, services, trades, homes and the many other sectors of society that do not touch healthcare in any significant way. Their stories of how they became involved in rare disease research are unique until they get to the part of their stories where they all say, “and then.” And then, their stories start to merge around efforts to find cures and treatments, which led them into research.

Rare disease patients, therefore, come to research from the bottom up, and they learn about research along the way. In contrast, the researchers they work with generally come to research from the top down through an interest in biomedical sciences and with formal training. Rare disease patients and research scientists have learned to work together and have successfully combined efforts to discover treatments and marshal them through to clinical adoption. However, natural tensions emerge when the bottom up meets the top down in research. Patient urgency meets researcher deliberate methods (“more research is needed”). Patient daring meets researcher risk aversion (tenure requirements, funding preferences). Patient push for novelty meets researcher resistance to change (adherence to existing concepts). Therefore, researchers who accept the invitation from rare disease communities needing help with research studies should be prepared to adapt to expectations driven by urgency, high risk tolerance and impatience with the status quo. Rare disease patients are looking for revolutionaries, not just puzzle solvers tinkering around the edges of established concepts. The right partner will recognize and reconcile these tensions.

RARE DISEASE PATIENTS AND RESEARCH SCIENTISTS HAVE LEARNED TO WORK TOGETHER AND HAVE SUCCESSFULLY COMBINED EFFORTS TO DISCOVER TREATMENTS AND MARSHAL THEM THROUGH TO CLINICAL ADOPTION.

THE RIGHT PROGRAMS ARE MORE THAN JUST DATA COLLECTION

Rare disease groups are experienced in research to some degree, but probably not extensively in the research regulators, clinicians and payers now require. Neither are they experienced working with scientists doing this kind of research. The right research program will, therefore, incorporate educational, structural and operational components.

Educational

Because the call for research to support rare disease treatment coverage policy decisions is relatively recent, many rare disease groups will need to be informed of these new requirements. I have witnessed shock, dismay and incredulousness on many occasions when patients first hear that payers require more justification beyond regulatory approval for coverage of orphan drugs. In addition, while many of the groups are extremely well versed on methods for discovery and translational research, they need background on research methods used for health economics and outcomes research. Therefore, for patients and groups not yet acclimated to these requirements, education and training on the need for this research and basic methods used are vital to their participation.

The educational component of the right research program, however, is bidirectional. Rare disease patients have important perspectives on their illness experiences. They can contribute to translating clinical endpoints used in trials to aspects of their lives that regulators can incorporate into their reviews and payers can more easily assess against the aims of their health plans. Patients can rank the importance of various features and benefits a particular product offers them, and thereby help bring more precision to research programs designed to assess patient value. By seeking patient input, researchers will likely garner valuable information that will strengthen and enrich their studies.

Structural

While mostly all rare disease groups are tightly connected to their constituents, variability exists in the degree to which they are able to collect the necessary research data. Even those groups with established registries may not be collecting the right information to meet the specific need, or they are unable to make necessary adaptations. Therefore, industry sponsors and research organizations engaging rare disease groups should be prepared to provide guidance in enhancing existing structures or creating new ones to gather the required data. These contributions could include supporting a registry *de novo* or enhancing an existing registry, collaborating with the group in designing the research plans and support materials for potential participants, and providing funding to support rare disease group personnel participation, among other activities.

Generally speaking, collaborations between industry sponsors or research organizations and rare disease groups have heretofore been narrowly focused on only what is needed for a clinical trial program, regulatory approval or post-marketing surveillance requirements. Patient groups, however, are often interested in a broader set of data spanning a longer period of time than the sponsor. Alas, they have to take what they can get. I thus feel compelled to make a plea to organizations working with rare disease patients to consider supporting the broader data needs and interests of the groups. Whatever form these collaborations eventually take, they obviously must comply with legal requirements and meet ethical standards, as well as outline agreed upon stipulations about who controls the data and how the data can be used.

Operational

A lot of the information useful to health economics and outcomes research can come from patients directly. Rare disease patients are highly engaged and often very willing to participate in studies and surveys. If anything, they may participate too much given the cries for mercy I hear from them every so often. This is all the more reason, then, to structure their participation so that individual patients or their caregivers can provide input in the easiest manner possible. The wide range of rare diseases yields a wide range of limitations; researchers need to understand that this will affect patient capabilities and preferences for a given research program.

Rare disease patients are becoming accustomed to being able to interact with data collection mechanisms such as registries. In particular, many of them expect that they can extract data of interest, and they often expect, or at least request, the ability to submit queries and run some analyses themselves to compare their situations with others in their cohort. At the very least, the groups will expect to see outcomes from the studies. My experience working with these patient groups indicates that allowing patients some access to data analysis and reporting activities strengthens overall trust and goes a long way in building stronger relationships.

THE OPPORTUNITY AWAITS

Requirements for data outside that normally gathered during clinical trials are presenting new challenges for rare disease patients in getting access to treatments. Like they did before when they had to stimulate and support discovery and translational research, rare disease patient groups are prepared to support the research necessary to address these new access challenges. But, also like before, these groups will need to form partnerships with industry sponsors and research organizations to generate the necessary evidence. Therein lies the opportunity for research organizations with capabilities in health economics, outcomes research, health services research, market access and like methods. The rare disease groups that are fortunate to have treatments — or the prospect for new treatments — will eagerly engage in these partnerships. The National Organization for Rare Disorders (NORD) is prepared to help facilitate these relationships and contribute to the methods and analyses that will ultimately improve patient access and innovation to rare disease treatments.

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Valuing Your Orphan Drug with Appropriate Evidence: Prepare Well and Get the Perspective Right

Jeff Anderson, PhD, Principal Consultant, Strategy Solutions, Evidera

INTRODUCTION

As more rare and debilitating diseases are identified, the need for new orphan drug innovations to tackle these conditions becomes more in focus. This is recognized by the increases in both market share and prescribing levels of orphan drug technologies over recent years.[1] However, impact on budgets of these orphan drugs is a growing concern for policy makers and payers.

To this end, decision makers are demanding greater quantities of evidence with an increasing level of scientific rigor[2,3] to demonstrate comparative effectiveness. In general, the high cost of orphan drugs is often in conflict with the perceived benefit of the product in relation to any alternative treatment and the consumption of the healthcare resource budget, given that rare diseases affect so few people.

Furthermore, competitive challenges among the crowded therapeutic marketplace have driven the need for not only greater payer scrutiny but product differentiation and comparative assessments.

Obtaining optimal product positioning and market uptake requires manufacturers to address the issues that will define product value. What is fundamental to this goal is generating robust, demonstrable evidence that is:

- At an appropriate depth and quality
- Relevant for the particular audience
- Produced at the most appropriate time in the product life cycle development

This is no different for orphan products targeting rare diseases. However, while many of these principles are well tested for non-orphan drugs, demonstrating the value of an orphan drug can be challenging from the various decision-making standpoints — policy makers, payers, patients and providers.

EVIDENCE CHALLENGES

Payer sensitivity is growing and this is understandable. Often questions are raised around the quality and appropriateness of the evidence to back up any value claims; economic models use assumptions based on this evidence, and hard endpoints such as health-related quality of life data may be missing. This creates greater uncertainty from the payer's perspective.[4] Additionally, payers have become increasingly skeptical if orphan drugs are initially reimbursed for a specific disease and later are extended to non-orphan indications. The result is payers often apply greater restrictions to orphan drug use, and it is suggested there is a clear correlation between lack of sufficient evidence and reimbursement rejection rates by payers.[5]

The *nature of the evidence* used to demonstrate value provides a wide range of challenges. Burden of illness and the level of unmet need may be difficult to establish as the natural history of the disease and definitions of rare conditions are not always clear. Data may be limited to only a few individuals with the condition. Linked to this, questions are raised about single-arm clinical trial designs, the choice or lack of appropriate comparators and the need to measure surrogate endpoints across short time horizons. There may be limited evidence on survival, function or feelings of individuals who live with rare diseases. Similarly, with these limitations in evidence, demonstrating cost-effectiveness and measuring the full impact on healthcare budgets is challenging.

Decision-maker assessment approaches to orphan drugs in different markets are not necessarily equivalent.[6] Some payers apply the same evaluation criteria to those they apply to non-orphan drugs (National Institute for Health and Care Excellence [NICE] or Scottish Medicines Consortium [SMC] in the UK, for example). Others adopt different criteria to recognize the differences in orphan drug value propositions (the Federal Joint Committee - Gemeinsamer Bundesausschuss [G-BA] in Germany, for example). Classification of an orphan drug varies between countries, primarily based on size of target population. Some assessments are fast tracked, whereas others are evaluated using currently established and thorough appraisals. Countries using evaluation methodologies such as cost-effectiveness (cost per quality of life year) could struggle to demonstrate the true value of orphan drugs as these approaches may not be sensitive enough to assess the budget impact and wider health gain on patients and their caregivers.

Targeting the evidence generation activity is an important consideration for manufacturers. Given the difference in payer approaches, early dialogue with key opinion leaders (both from a clinical and reimbursement perspective) in each market will be key in guiding decisions around the right evidence needed for the right audience at the most appropriate time. This will crystalize any plan to generate evidence, adopting the right balance and focus of evidence. For instance, some payers will favor a stronger underpinning argument around the clinical effectiveness of an orphan drug product in a particular indication. Others will need to see both cost and clinical effectiveness comparisons to current standard of care.

EVIDENCE REQUIREMENTS IN VARIOUS MARKETS

The table below represents a practical approach for manufacturers to begin to appraise their position with regard to the evidence requirements in any particular market. Early dialogue with payers and other key opinion leaders will help to detail the right evidence for the right audience at the appropriate time.[7] It will be clear if the data and other evidence that manufacturers have at their disposal matches the key requirements for future payer decision making.

GENERATING THE RIGHT EVIDENCE FOR THE RIGHT AUDIENCE IS A SYSTEMATIC AND EVIDENCE-BASED PROCESS.

Table 1: Example of how a manufacturer might develop an evidence framework for its product

Decision maker criteria in target market	What evidence is needed / appropriate?	What evidence is available now?	What are the evidence gaps?	What studies should be undertaken to fill the gaps?	Timings or associations	Strength of argument / position
Burden of Illness / unmet need						
Clinical value						
Economic value						
Outcomes value						
Unique HTA requirements						

SYSTEMATIC AND EVIDENCE-BASED APPROACH TO DEMONSTRATING VALUE

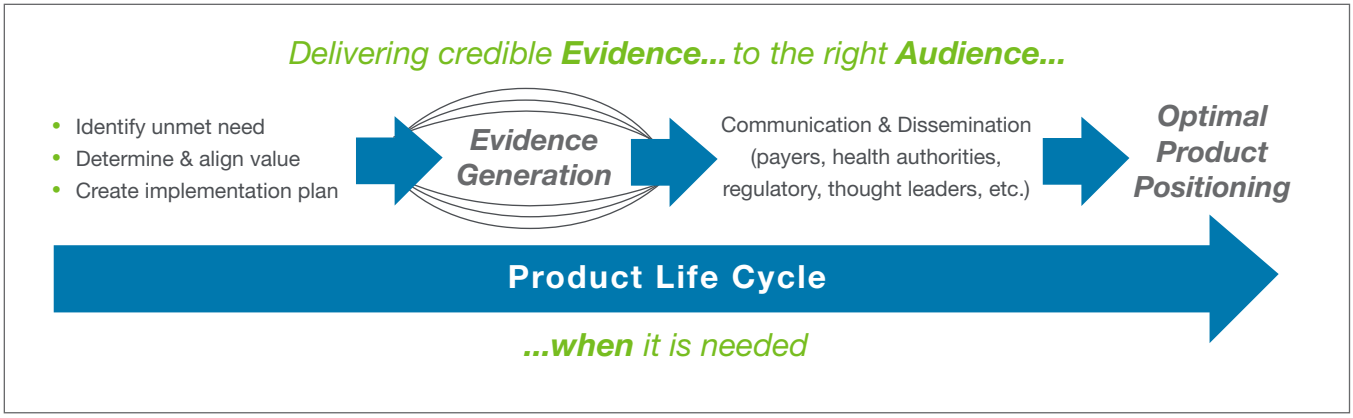
The approach to determining the value of a drug with orphan status is equivalent to that of non-orphan drugs, even if the nature and balance of the evidence required may vary in different markets. Generating the right evidence for the right audience is a systematic and evidence-based process whereby manufacturers need to:

- Understand what the burden of the rare disease is and what needs to be the product value focus, given the target market and payer evaluation process
- Understand what evidence is required, to what detail, and what is currently available within the organization and how any evidence gaps should be filled
- Design and develop appropriate, defensible and tailored value messages for each market

SUMMARY

Manufacturers need to remember that there may be a requirement for greater evidence generation investment in the rare disease space, both before and after product launch. They will need a greater understanding of payer responses to different levels of the value story. To this end, early engagement in constructive dialogue with payers and other orphan drug stakeholders is recommended, together with earlier involvement of HEOR activity in the

Figure 1: Illustration of evidence planning approach for orphan and non-orphan drugs



evidence generation process, e.g., development of patient-reported outcomes (PRO) instruments and defining and agreeing on meaningful, patient-centered endpoints to inform trial design and economic model parameters.

Earlier commentary on orphan drug reimbursement decisions suggests that different value messages (or combinations of) may be more appropriate and should underpin any developing evidence and market strategy. For example, clinical effectiveness evidence, impact on clinical practice or patient outcomes, or detailed budget impact may be more appropriate than cost-effectiveness comparisons alone. There is also recognition that the traditional evidence base associated with drugs with non-orphan status may need to be supplemented by strong arguments around clinical effectiveness and patient equity/access in the orphan drug arena. This has additional implications for orphan drug pricing given the level of reimbursement support for individual patients locally.

Finally, effectively addressing these issues requires a comprehensive, multiyear, multidimensional strategy to document and communicate evidence of product value. The key is to be creative while establishing a standardized and consistent value demonstration methodology as part of an orphan drug product strategy. This will facilitate and optimize coverage, reimbursement and market adoption.

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The Evidence Requirements for Orphan Drugs From a Payer Perspective: Is the Bar Raised or Lowered?

Karen Sandman, PhD, U.S. Practice Lead, Payer Communications, Evidera

This issue includes discussions on a variety of methodologies to study epidemiology, patient-reported outcomes, comparative effectiveness and healthcare decision-making in rare diseases. One question that comes to mind is, "Do we need all this? If a disease is rare enough, and severe enough, doesn't the unmet need speak for itself?" If only it were so easy! As anyone who has worked in rare diseases in the past decade can attest, the "glory days" of easy market access for orphan drugs — if they ever existed — are over.

Certainly, there are many healthcare systems, such as those in Germany and Australia, that evaluate treatments for orphan diseases differently than those for more common conditions. Most payers recognize that orphan drugs have high prices because the cost of developing the drug and keeping it on the market is not proportional to the size of the target population, and manufacturers need to price sufficiently high to maintain profitability — and thus to be able to provide the drug to the patients who need it. Despite understanding the unique aspects of orphan diseases, payers also are managing finite healthcare resources, and there has been a steady uptick in the number of orphan drugs on the market in recent years.

The balance between the desire to provide equitable treatment to patients with rare diseases and the need to contain healthcare spending leads to a set of evidence requirements for orphan drugs. The core principles of market access apply regardless of the disease: The manufacturer needs to make a clear case for burden of illness, unmet need, clinical efficacy and safety, comparative effectiveness, patient-relevant outcomes and economic value. Let's take a look at some typical objections raised in the case of rare diseases and how evidence might help to address payer concerns.

How solid are your prevalence estimates? How do I know the target population is not going to creep up to higher levels, especially now that the awareness will be higher and there may be more diagnostic testing?

Manufacturers often communicate to payers that the budget impact of an orphan drug will be low based on the very small size of the target patient population. For this economic argument to be compelling, however, there must be strong confidence in prevalence estimates. Getting solid epidemiology figures in rare diseases can be challenging, and oft-cited literature-based estimates may be based on outdated data or questionable assumptions. For maximum credibility, it is advisable to use current, scientifically rigorous prevalence estimates, particularly when these estimates will support an economic analysis.

Another emerging issue is related to genetic testing. Many rare diseases are genetically based, and there can be a broad range of disease severity depending on the specific genetic variant that a patient has. With increased disease awareness and the broader availability of genetic testing, there may be more patients genetically diagnosed with a rare disease who would not have been diagnosed according to standard clinical criteria. Payers may therefore be concerned about the potential for the target population to creep up to higher prevalence levels, with increasing budget impact. In these situations, it is critical to reinforce the commitment to appropriate use. Prospective observational studies of patients with less severe phenotypes may help to establish the disease burden and better elucidate appropriate treatment for these patients.

The standard of care in this disease is "watch and wait," and I am not convinced that patients need a more aggressive treatment approach.

For many rare diseases, the standard of care has been defined not by evidence-based medicine, but by the lack of suitable treatment options. Despite evidence demonstrating the efficacy and safety of a new product, there may be a perception that patients do reasonably well without active treatment.

To address this perception, it is necessary to assess the true clinical burden and unmet need in the rare disease. Perhaps disease pathology occurs much earlier in the patient's life than had been thought, and the process could be prevented or slowed by appropriate disease-modifying treatment long before the onset of severe signs and symptoms.

In some cases, a careful and comprehensive review of the literature will provide sufficient evidence on disease progression. In other cases, a detailed chart review or other type of real-world study can reveal the true clinical burden and unmet need in a rare disease. Disease simulation models can also be useful tools to correlate disease pathology with long-term clinical consequences.

The efficacy data are limited to 1 year. We need longer term data to evaluate the benefits and risks of this treatment.
ager to bring an effective product to patients with limited treatment options, orphan drug manufacturers often submit relatively short-term data for regulatory approval. While some payers will reimburse based on shorter term results, others may expect longer term data before making a final coverage decision.

Certainly, extension studies and registries can provide the longer term efficacy data being sought. To the greatest extent possible, the long-term extension studies and registries should include payer-meaningful outcomes such as resource utilization, patient-reported outcomes and long-term safety.

You are showing me efficacy based on an endpoint that I can't correlate to real life. Does this endpoint translate to increased survival? Decreased resource utilization? Pain reduction or improved quality of life?
Orphan drugs may receive approval based on a biologically relevant, surrogate endpoint that is clearly correlated to the product's mechanism of action. While this makes great scientific sense, payers want to use their resources to treat patients, not proteins. Ideally, the pivotal trial should be designed to capture outcomes that are meaningful from a clinical, humanistic and economic point of view.

If the pivotal trial has already been designed and the endpoints do not cover all of the relevant topics, there is a need to connect some dots. Can you use real-world evidence to show the correlation between the trial's primary endpoint and some more meaningful outcomes? Would patient interviews or vignettes demonstrate the relevance of the surrogate endpoint? Ultimately, the payer needs to feel confident that the drug's value can be measured in patient-relevant terms, and this information is also critical for developing a robust economic analysis.

The economic analysis is not sufficiently robust: The inputs of the model rely on assumptions that are inadequately justified (e.g., utility values, survival benefit, likely underestimate of costs, assumptions regarding the product alleviating the need for other standard supportive treatments).
Ultimately, if there is a strong base of evidence relating to burden of illness, unmet need, clinical efficacy, safety, comparative effectiveness and patient-relevant outcomes, then it should be possible to develop a robust and credible economic analysis of the treatment of an orphan disease. As outlined earlier in this article, there are places where all of these types of evidence can fall short, especially in the case of orphan diseases, where literature may be sparse and available patient data may be limited. By taking a proactive and thoughtful approach to building the evidence dossier for an orphan drug, it should be possible to support a compelling value proposition.

So … is the bar raised or lowered?
Getting back to the original question: Is the expectation for evidence supporting an orphan drug higher or lower than that for products used in more common diseases?

IDEALLY, THE PIVOTAL TRIAL SHOULD BE DESIGNED TO CAPTURE OUTCOMES THAT ARE MEANINGFUL FROM A CLINICAL, HUMANISTIC AND ECONOMIC POINT OF VIEW.

Instead of having to differentiate a product in a crowded primary care market, often with generic competition, manufacturers of orphan drugs are faced with the challenge of finding difficult-to-obtain evidence, which requires a good deal of planning and foresight. Ultimately, though, payers are looking for the same types of evidence regardless of how many patients are affected by the disease: Does this product safely and effectively address an unmet medical need, and is its cost acceptable within the constraints on how we spend our healthcare funds? I don't think the bar is necessarily higher or lower for orphan drugs, but perhaps it is zig-zagged, with some areas more challenging and others less so.

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Working Together to Enhance Rare Disease Research — The Role of Patient Advocacy Organizations

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CHALLENGES OF RECRUITING FOR RARE DISEASE STUDIES

There are more than 6,800 conditions listed in the National Institutes of Health's Office of Rare Diseases Research, and approximately 8,000 rare diseases that affect millions of individuals worldwide. Rare disease research is currently the fastest growing area of drug-related research and development.[1, 2] Due to the low number of individuals with a specific rare condition, successful and cost-effective research designs and methodologies that are sensitive to the unique requirements of the disease are challenging.[1] In order to design studies that support the development of treatments for individuals with rare disease, it is important to carefully consider the following two key research elements:

1. **The careful design and planning of research methods for patient recruitment and data collection**

   Rare diseases pose unique challenges to study planning and patient recruitment due to their inherent low patient numbers.

2. **The selection of meaningful trial endpoints (including patient-reported outcomes) for the target population**

   Stakeholder groups (regulators, payers, policy makers, and patients) are calling for drug development programs to be increasingly patient-focused.[2] In order to adequately define and select the target population, it is important for researchers to have a good grasp of what meaningful endpoints need to be measured.[3]

This article seeks to identify and focus on the challenges of study planning and recruitment and to provide potential solutions through strong collaborations with patient advocacy organizations (PAOs).

TRADITIONAL PATIENT RECRUITMENT METHODS AND CHALLENGES

Researchers in rare disease populations have traditionally followed the same patient recruitment methods used in more common disease areas, such as recruiting patients via hospitals or medical clinics, recruiting agencies, newspapers and websites or social media pages.[4] When using these methods to develop, inform and/or validate endpoints or obtain key insights in a rare disease population, however, there can be several potential challenges to successful recruitment. These challenges stem from the limited pool of rare disease patients in any given area or location, making it difficult to enroll an adequate sample from only a few sites, hospitals or cities. In order to achieve the desired sample, data collection may need to be expanded to several times the number of sites, or even additional countries, compared to what is needed in more common disease areas. This process can greatly increase both the time and the expense required for execution of the study.

Screening and properly identifying eligible rare disease patients pose challenges as well. A planned recruitment strategy can play a major role in the effort required for identifying eligible patients. For example, newspaper advertisements viewed by a general population often elicit responses from individuals who are not diagnosed with the target condition, which increases the screening burden. Additionally, if the perspective of a clinician or observer (including caregivers, parents, spouses, etc.) is required, recruiting clinicians and/or observers can also increase the screening burden by requiring the coordination and/or necessity of the participation of both parties.

With these challenges to recruitment and screening in rare disease populations for endpoint development/validation or obtaining key insights, it is important to explore innovative methods for recruiting within a rare disease population and capturing high-quality, informative data. One such method that has increasingly shown promise is a strong collaboration with patient advocacy organizations (PAOs) to recruit patients, observers and/or clinicians for these rare disease studies.

HOW CAN RARE DISEASE PATIENT ADVOCACY ORGANIZATIONS HELP?

The Impact of Rare Disease PAOs

Currently, there are more than 1,300 rare disease organizations in the United States alone that support the efforts of furthering an understanding of rare diseases in some way.[5] Typically, rare disease PAOs focus their resources on either assisting patients and families or contributing funds/efforts to research that will further 1) understanding of the disease process, 2) development of diagnostic tools, 3) development of preventative interventions, and/or 4) development of treatments.[1]

Due to the rarity of these life-altering diseases, patients and their families often feel isolated from others with the disease or become frustrated over the lack of information or support available.[1,6] As a result, patients and their families typically turn to either rare disease PAOs or to rare disease umbrella organizations for support. Rare disease umbrella organizations include the National Organization for Rare Disorders (NORD), the European Organization for Rare Diseases (EURORDIS), Orphanet and the Genetic Alliance (*Table 1*). In particular, rare disease umbrella organizations play a huge role in furthering the objective of the rare disease PAOs by joining with PAOs to provide the assistance they need to develop and implement research strategies.[7] In addition, these umbrella organizations also advocate for policies that address the needs of the patient and their families, or focus their efforts on collecting information from expert centers, laboratories and ongoing research projects in order to make this information available within the rare disease community.[6,8]

Most rare disease PAOs also support patients by focusing on their education and the education of their families, and/or the treating clinicians, and connecting patients with skilled physicians.[8] With such assistance in navigating the rare disease landscape, it is easy to see how pivotal and central these organizations have become to the life and well-being of the patients, families and treating physicians.

WORKING WITH RARE DISEASE ADVOCACY ORGANIZATIONS TO FIND AND COLLECT DATA

Establishing a Successful Partnership

In order to establish relationships with PAOs, it is essential to identify the key contacts within the organization. Umbrella organizations typically offer listings and contact information for a majority of rare disease PAOs on their websites, making them a great source to identify the point of contacts at the PAOs that focus on the rare disease of interest. Typically, the points of contact for these organizations are members who are serving as the organization president or a member of its board of directors. As geneticists, clinicians, researchers, public health officials and people who have been personally impacted by the disease (either through their own experiences or the experiences of someone they know), they can provide valuable insight to the design and planning of a research study for rare diseases.[1,9]

Communicating Study Objectives and Understanding PAO Goals

Once a relationship with a PAO is established, the ability to effectively plan a recruitment strategy with the help of these organizations is dependent upon two factors: 1) transparent and effective communication of study objectives with the PAO, and 2) a sound understanding of the goals of the PAO. Including the PAO in the research planning process will help create a mutual partnership where both engaged parties have a vested interest in seeing the research move forward *(Figure 1)*, and increase the informed patient-centeredness of the study to best reflect the needs, values and role of the patient with this rare condition.

Transparency with the organization at the onset is essential. Providing information on the goals of the endpoint study and recruitment needs will offer the PAO an overview of the study and allow it to determine

Table 1

LISTING OF RARE DISEASE UMBRELLA PATIENT ADVOCACY ORGANIZATIONS
Canadian Organization for Rare Disorders
European Organization for Rare Diseases (EURORDIS)
Genetic Alliance
Japan Patients Association (JPA)
Korean Organization for Rare Diseases
National Organization for Rare Disorders (NORD)
New Zealand Organization for Rare Disorders (NZORD)
Organization for Rare Diseases India
Orphanet
Taiwan Foundation for Rare Disorders

whether its goals are aligned with research study goals. Different PAOs have different areas of focus when it comes to furthering the progress of appropriate care and treatment development for a rare disease, and therefore, having a general understanding of the research study could help them see whether their resources will meet the needs of the study.

An early understanding of a PAO's organizational structure and function is important to the planning process for a several reasons. First, it is important to consider the PAO's focus and networking capabilities, as this will determine its ability to reach the target population. For example, PAOs that offer frequent opportunities for members to commune and interact, such as frequent in-person meetings and/or conferences, may be able to provide easy on-site recruitment access, thus increasing the possibility of collecting data in shorter time frames. A second consideration is the number of platforms the organization uses to connect with its patient population. Access to multiple platforms, such as email lists, websites, group venues or social media (e.g., Facebook, Twitter) increases advertising opportunities to individuals with the rare condition and their families throughout the duration of a study.

Recruiting via PAO Community Networks

After learning about the goals and organization of the PAO and discussing the goals of the study with the PAO, researchers and the PAO contact person can collaborate to identify possible recruitment strategies. Many rare disease patients become motivated to get involved with community networks within a PAO, which makes the PAO an excellent source of identifying people with a specific rare disease. *Table 2* lists some of the resources that a PAO may have available to help researchers identify potential subjects. These existing sources of potential research subjects can be a great asset for study recruitment. Recruited subjects can be invited to participate in any study type (e.g., cross-sectional survey, qualitative interviewing, observational or interventional trial). Most importantly, due to the continued close-knit connections that these rare disease PAOs have with patients and their families, PAOs have the trust of the patients and families involved.

Mutual Respect and External Influences

When working with PAOs, it is important to note that these organizations can be protective of their members and may perceive outside interventions as conflicts of interest or invasions to the privacy of their members. People with rare diseases and their families trust these organizations; therefore, it is important to respect these boundaries and to fully cooperate with any requested procedures when communicating with the membership. For example, many PAOs work hard to host patient conferences that allow patients, their families and clinicians to come together and learn about the disease. Not surprisingly, many PAOs will request that researchers interested in enrolling, interviewing, surveying, etc., not approach the patients and families during patient conferences and not schedule any research activities during the conference proceedings. In this instance, a well-planned strategy and transparent communication will ensure that both the needs of the PAO and the needs of the research study are met.

Figure 1

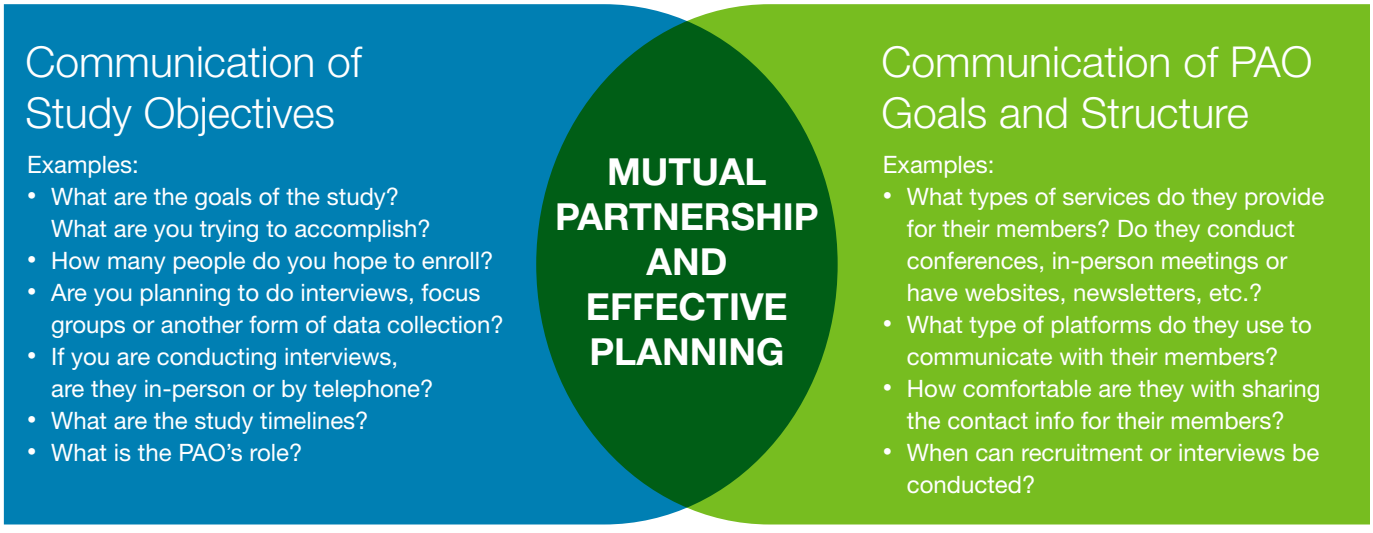

Table 2

PATIENT ADVOCACY ORGANIZATION (PAO) RESOURCES FOR IDENTIFYING STUDY SUBJECTS
Rare disease websites and social media outlets
Patient databases
Community group and PAO electronic mailing lists (listservs)
Clinical sites and geographic areas with high patient concentrations
Listings of clinicians who treat patients with specific rare diseases
Rare disease conferences
Rare disease websites and social media outlets

Another significant consideration is that there may be external influences beyond the researcher's control. PAOs may be approached by multiple groups interested in conducting research studies among their membership. As a result, the PAO leadership must consider whether multiple research study requests will overwhelm their members, and the PAO may prioritize these requests. Additionally, the research objectives and strategies of a PAO may be influenced by financial resources, availability of effective treatments and the experiences and priorities of the group's founders.[1] Awareness of potential road blocks early on in the research process can help mitigate any unexpected burden to the endpoint research budget and timeline.

CONCLUSION

The challenges presented in studying rare diseases require innovative methods and out-of-the box thinking that can be addressed through collaborations with rare disease PAOs and umbrella organizations. The solutions that come from these partnerships can serve to be both cost-effective and time-efficient when conducting research in rare diseases. PAOs can help researchers identify the target population, conduct screening activities and involve patients, observers and/or clinicians in research. These organizations offer valuable resources and can provide expertise as lifetime partners in research efforts to better understand rare diseases and aid in the development of treatments to enhance and extend patients' lives.

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Meta-Analysis in a Rare Disease Setting: When is the Evidence Enough and What is the Most Appropriate Approach?

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While a rare disease, by definition in the European Union (EU), affects not more than 5 per 10,000 inhabitants, the aggregate burden of many such diseases is vast; in the EU alone, *an estimated 5,000–8,000 rare diseases affect approximately 27 million to 36 million people.*[1] Given this substantial population, decision making about reimbursement of treatments is beset by multiple challenges and has been keenly debated among various stakeholders, including policy makers, third-party payers, physicians, patients, health economists and ethicists. [2,3]

Development and evaluation of an evidence-based value story are often problematic in rare disease settings, particularly given the limitations in clinical trial design. Challenges include patient recruitment, small sample sizes, short durations of follow-up and a lack of head-to-head comparisons, any of which may impede the use of meta-analyses to assess comparative effectiveness. Although recent research indicates that orphan drugs are increasingly being evaluated in randomized controlled trials (RCTs), these studies are much rarer than observational studies and case series of patients with such conditions. Several recent reviews of health technology assessment (HTA) reports,[4,5] including assessments by the Institute for Quality and Efficiency in Healthcare (IQWiG),[6] found that consistent methodological specifications for generation of evidence to support HTAs have not been developed and implemented.

Recently, Evidera's Meta Research group has undertaken evidence generation projects in rare disease settings and has gained practical

experience on the synthesis of evidence through assessments of observational studies, case series and prospective clinical studies including RCTs, and in the application of various quantitative analytic methods for evaluation of comparative effectiveness as appropriate. In this article, we will discuss the lessons learned from our experiences. We hope to initiate a discussion of the best approach for gathering and evaluating clinical evidence using appropriate statistical methods — our goal being to inform HTA submissions and economic models for reimbursement agencies.

DON'T UNDERESTIMATE THE POWER OF CASE SERIES

The literature on rare diseases often begins with case reports. But over time, papers detailing case series — for instance, all patients seen with a specific rare disease at a given hospital over the last 20 years — have become more common. As clinicians develop an improved understanding of the pathology of the disease and approaches to its treatment, case series may eventually represent a fairly large evidence base. Literature-based research data from case series are typically considered to be lower-tier evidence[7] with a higher risk of selection bias. However evidence can be particularly valuable in a rare disease setting, especially in areas where higher-tier evidence is limited or unavailable. For example, case series that detail the experiences of every subject with the disease in a given location can be relatively free of selection bias and offer a valuable historical control that can also serve to inform the design of prospective clinical trials.

Naturally, it is important to assess the study quality in relation to the research questions being asked and, in particular, to tease out potential selection bias as one hopes to ensure the generalizability of the data collected. Following a systematic assessment of potential biases, various statistical analyses can be employed to reveal the disease progression patterns based on patient-level data selectively collected from case series. Such analyses could be used to better understand outcomes associated with standard of care management, determine adequate length of follow-up and/or provide information on what size of treatment impact would be necessary with a new drug. All these results can play critical roles when designing a costly prospective trial and potentially increase the likelihood of a successful trial outcome. For example, when population data is scarce, such analyses can be used to support and validate the results of an existing trial within a broader context.

FOLLOWING A SYSTEMATIC ASSESSMENT OF POTENTIAL BIASES, VARIOUS STATISTICAL ANALYSES CAN BE EMPLOYED TO REVEAL THE DISEASE PROGRESSION PATTERNS BASED ON PATIENT-LEVEL DATA SELECTIVELY COLLECTED FROM CASE SERIES.

It may be feasible to pool data across prospective single-arm studies and RCTs

Many rare diseases involve biochemical laboratory assessments; such assessments are often particularly important for inheritable rare diseases. Since the laboratory values do not involve subjective assessments, for which both pre- and post-values are often available, it may be reasonable to directly compare results from two different studies (RCTs or single-arm trials) evaluating different treatments. In such cases, certain arm-level effects (such as pre-post change scores on laboratory tests, either in absolute or percentage terms) may be similar across studies, for some outcomes, where controlling for a varying placebo effect may not be important. Essentially, we may be able to make the assumption that absolute, arm-level effects are "exchangeable," while the traditional meta-analyses make the weaker and usually more reasonable assumption that relative effects, i.e., *differences* between treatments, are exchangeable.

However, there may be no reason to suspect that changes in certain laboratory values should be lower or higher for different studies within the patient population of interest. We wish to emphasize that should this course be taken, it is critical that studies included in analyses are clinically and methodologically homogeneous, as differences in study populations or methods that affect absolute outcomes are not controlled by design.

Alternative statistical approaches such as MAIC or STC may be appropriate

When treatment comparisons are necessary, the literature is insufficient to allow for an adjusted indirect comparison, and a "naïve" indirect comparison is ill-advised because of population heterogeneity or other issues, alternative methods can be considered. For example, Matching-Adjusted Indirect Comparisons (MAIC)[8] or Simulated Treatment Comparisons (STC),[9] if sufficient data is available (especially individual patient data), allow one to build a more valid indirect comparison between two treatments. These approaches are not a panacea; two studies on two very different and non-overlapping patient populations are unsuitable for these methods, but when there is significant overlap, they may offer opportunities for comparison that would otherwise be lacking.

Concerns about availability and accessibility of orphan drugs, which are valid in many instances, do not imply that the current orphan drug policy framework is deficient but that the means of assessment needs to be improved upon for realistic and affordable payer prices to become the norm.[10,11] From our experience, a strategic and systematic assessment of the literature landscape can address payer and regulatory questions that may be otherwise answered through additional or extended RCTs. Well thought out, systematic data collection and selection has yielded reliable and defendable solutions in the rare disease setting. There needs to be an extension of the current criteria for value assessment to allow meaningful and robust benchmarks around rare disease cost and quality of life within the context and peculiarities surrounding rare disease evidence reporting and the diseases themselves. Policy should continue to evolve in the support of clinically and methodologically sound evidence generation, outside the realm of additional clinical trials.

A complete understanding of the existing available data and how the available information can facilitate clinically appropriate evidence generation is a powerful and cost-saving tool during the clinical development process. This early initiation of an evidence generation plan can serve multiple facets especially within the rare disease setting. Whereby the knowledge and appropriate selection of published clinical research can support evidence generation through indirect treatment comparison via standard meta-analyses or, alternatively, other statistical analysis methods such as those described above. Results of such evidence generation can help avoid extended trials, support existing trials or demonstrate additional clinical trials may not be necessary. Ultimately, intelligent, innovative evidence synthesis has and should continue to assuage some of the payer and regulatory challenges in order to better provide patients in the rare disease setting timely treatment options.

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Estimation of the Prevalence of Very Rare Diseases Based on Data From Specialized Treatment Centers: Approaches for the Identification of the Reference Population

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Studies of very rare diseases (less than 1 in 100,000 of the general population) often use cases seen at specialized centers. While the estimation of the disease prevalence based on data from such studies is typically complicated by multiple potential sources of both systematic error and random error, establishing the reference population is a key challenge. We discuss several approaches for the estimation of the reference population and give examples based on a study of Multicentric Castleman Disease (MCD).

FACTORS THAT COMPLICATE PREVALENCE ESTIMATION OF RARE DISEASES

- In rare diseases with non-simple diagnoses, a large number of cases are undiagnosed, or diagnosed with great delay. The true number of cases in the population is likely higher.
- Often diseases were not well studied; diseases' natural history and duration are not well-known.
- Only a small number of centers and patients are available for study.
- Centers that treat a relatively large number of patients are specialized centers or known centers of excellence and serve as referral rather than regional centers. There is not, therefore, a well-defined geographical area where patients are coming from.
- Patients will travel long distances, or even relocate to seek treatment.
- Diseases may be related with certain ethnic or racial backgrounds, environmental, occupational or behavioral factors. These may be associated with geographical areas and vary by the location of centers and complicate generalization of prevalence estimates.
- It might be impossible to distinguish true incidence and prevalence from referral patterns or access to care.

STUDY EXAMPLE — MCD

Multicentric Castleman Disease (MCD) is a rare lymphoproliferative disease with no established therapy and of unknown origin that involves the overproduction of the cytokine interleukin-6 as one of the key pathogenic processes.[1] MCD patients are often heterogeneous in signs and symptoms, some of the more frequent being fatigue, night sweats, fevers and anemia. Chronic therapy and optimal disease control are the present clinical practice and goal, respectively.[2,3]

Adult patients with a confirmed MCD diagnosis between Jan. 1, 2000, and Dec. 31, 2009, from two major referral centers that specialize in treating MCD — Mayo Clinic (Mayo Clinic; Rochester, MN) and the Fred Hutchinson Cancer Research Center (FHCRC; Seattle, WA) — were included, and their electronic medical records were abstracted. One of the study objectives was the estimation of the disease prevalence.

Assessment of the Reference Population through Catchment Area

The catchment area defines the area from which patients will most likely be referred to the specific center and, therefore, included in the data. The reference population for each center can therefore be assumed to compose the residents of the catchment area. The reference population can be estimated using U.S. Census data.

In our study, analyses were performed using ArcGIS and Census 2007 data. Stratification by age, sex, race, ethnicity and educational attainment was based on the Census 2000 data.

The maps in the figures display the location of MCD cases identified by the two centers and catchment

areas assessed through different approaches. Cases for each center are represented by a dot. The location for the patient was available only as the 3-digit ZIP code area they resided in at the time of diagnosis. Therefore, the locations of the dots displayed on the maps were randomly placed within each representative 3-digit ZIP code area by ArcMap.

We assumed that the changes in the states' population over the six years prior to 2007 and the two years post 2007 were not significant for the estimate. Generalization of the results to estimate the national prevalence of the disease will have to either assume that changes over the study time to local populations were similar to the national ones, or take them into account in the calculations.

In addition, the two centers are well-known centers of excellence, and patients might not represent the general patient population. Differences in distributions of risk factors such as gender, age, HIV status and other disease risk factors might vary between the centers' population and the general population, complicating the generalization of the estimates.

Assessment of the Catchment Area

Spatial Distribution of Cases in the MCD Study

The Mayo Clinic seems to serve as a referral center, with cases originating from a vast geographic area *(Figure 2)*, including two cases from Washington state. The Mayo Clinic cases were based in ZIP codes from 16 states, with no state represented by more than five patients.

Most patients from the FHCRC center were located in ZIP code areas in Washington state and Oregon *(Figure 2)*. One patient from the FHCRC center with a Washington state area code did not have a ZIP code available and he was assigned to the most common ZIP code.

Regional-Based Catchment Definition

Regional-based catchment definitions could be based on observed spatial patterns in the data or on information about referral patterns from the institute or other sources.

The catchment area for the FHCRC was defined based on clustered MCD cases in the states of Washington and Oregon. These states also had by far the highest prevalence proportion at one to two MCD cases per million population *(Figure 1).* The FHCRC did not catch all MCD cases from within Washington and Oregon (in fact two cases in this area were identified by the Mayo Clinic); however, the spatial clustering of cases in these two states is reasonable justification for the definition of the catchment area. A decreasing gradient with distance along the West Coast was apparent. Washington state cases and population can therefore be used, by this approach, as the basis for the prevalence estimate. Many cases are likely not represented in the data, even within the catchment area (by any definition), and due to the difficulty of diagnosis, and possibly lack of access to care, many MCD patients are likely never diagnosed. The estimates are therefore best used as a lower limit to the likely true number of MCD cases, and the estimates based on areas with higher prevalence are likely closer to the true prevalence.

Driving-Distance-Based Catchment Areas Definition

Catchment areas based on driving distances by categories are presented in *Figure 2*. Thresholds could be chosen by assumptions regarding the time period most patients would be willing to travel.

Cases-Clustering-Based Catchment Areas

We used the "Hotspot Analysis" tool in ArcMap to define catchment areas for each center based off of the 10-year period prevalence proportion for each 3-digit ZIP code area. Spatial relationship was based on inverse distance squared (strong punishment for increasing distance,

Figure 1

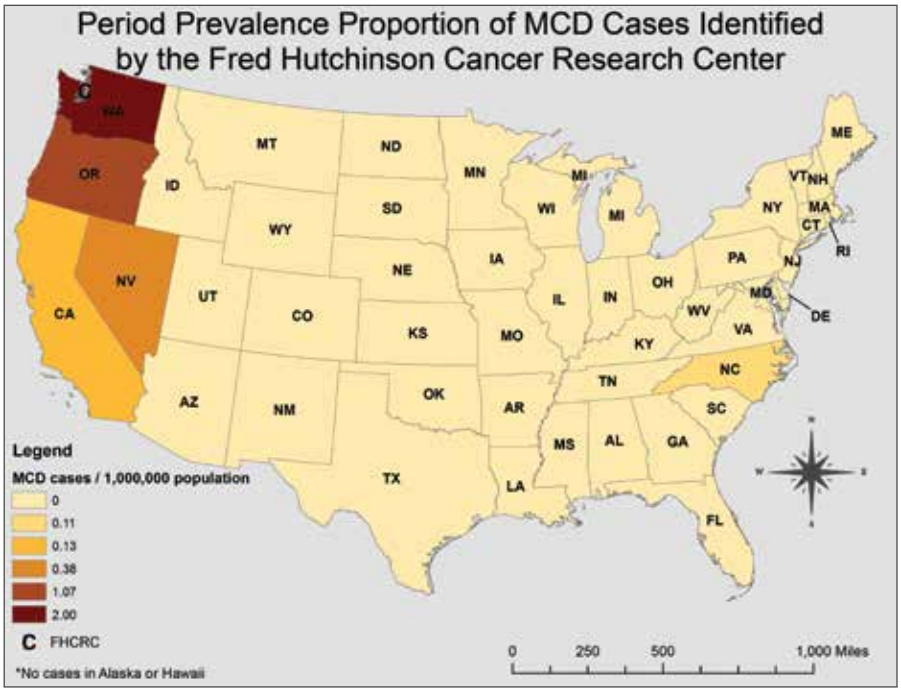
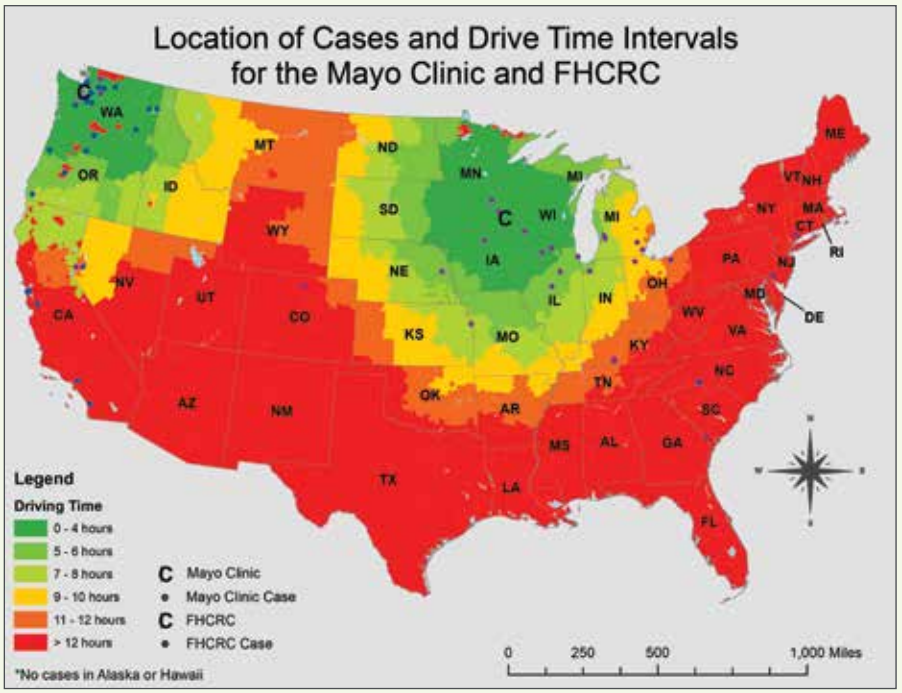


Figure 2



as we believed increasing driving distance to the center would be a barrier to treatment). The distance method used was the Manhattan distance that accounts for people traveling by roadways.

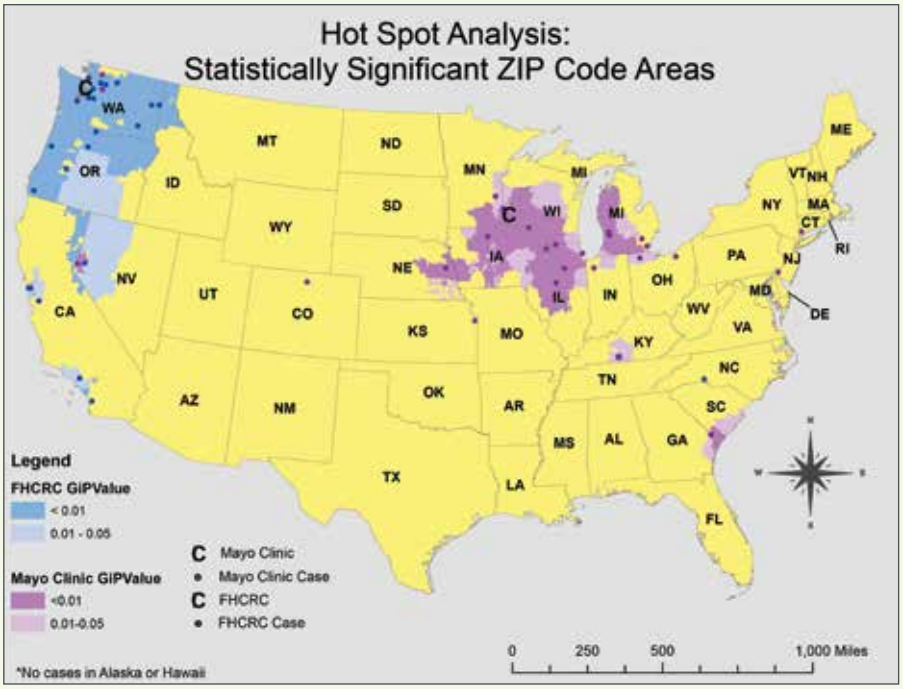
ArcMap uses this information to generate a Z-score. The significance level of the Z-score (areas where Z>1.96; p<0.05 indicate a cluster) is displayed in *Figure 3*. We considered the contiguous cluster around each center to be the catchment area.

The 10-year period prevalence proportion was calculated for each 3-digit ZIP code area by dividing the number of cases by the total population estimated by Census 2007 data (period prevalence per million population = MCD cases / 2007 population × 1,000,000).

Results from the broader study of patients' education level and their location indirectly supported this definition of catchment area. We compared patients' education grouped into two levels for Mayo Clinic patients (for which education-level information was available for all patients). Education of the adult population was compared by location within and outside of the catchment area. A significantly higher percentage of patients with higher levels of education (graduate/professional degree or higher) compared to the general adult population in the area traveled from outside of the catchment area to receive care at the center. This was not the case for patients with a lower level of education, and was not the case for patients with higher education within the catchment area. These results could suggest that broad socio-economic strata were using the Mayo Clinic for their care, whereas those from more distal locations tended to be from higher education (and likely income) strata.

A SIGNIFICANTLY HIGHER PERCENTAGE OF PATIENTS WITH HIGHER LEVELS OF EDUCATION (GRADUATE/ PROFESSIONAL DEGREE OR HIGHER) COMPARED TO THE GENERAL ADULT POPULATION IN THE AREA TRAVELED FROM OUTSIDE OF THE CATCHMENT AREA TO RECEIVE CARE AT THE CENTER.

Figure 3

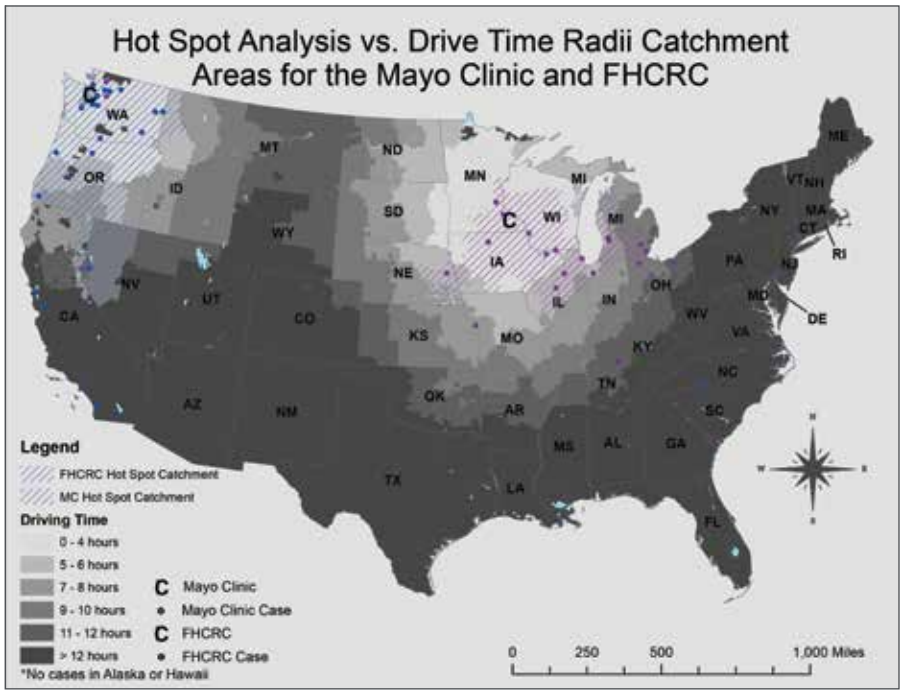


SUMMARY

There is significant overlap among the catchment areas defined by the different methods (*Figure 4*).

The "hot spots" based catchment areas at a 0.05 significance level are influenced by the population density in an area, and therefore areas that are sparsely populated but with close proximity to a center, or in certain geographical areas, might not be included in catchment areas by this approach.

Figure 4



EVEN WITHIN THE SAME CENTER, CATCHMENT AREAS MAY DIFFER FOR DIFFERENT DISEASES ACCORDING TO DISEASE RARITY, IMPACT ON PATIENTS' LIVES, REPUTATION OF THE CENTER AND OTHER FACTORS.

The most appropriate choice would depend on the study design and objective and on the data. The regional-based approach is the easiest to implement and could offer a simple solution for a rough estimate. The choice of approach for the estimation of a catchment area should also be determined by the characteristics of the disease in question and of the participating centers. Even within the same center, catchment areas may differ for different diseases according to disease rarity, impact on patients' lives, reputation of the center and other factors.

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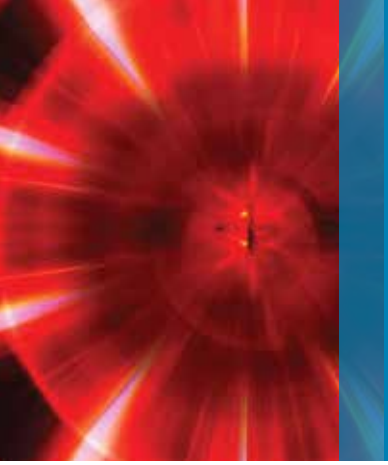

If Your Alpha Coefficient is "Flashing Red," Check Your Model!

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The old marketing slogan, "One size fits all," has never been entirely true. Many of us confirm this every time we go shopping for clothes. The same reality confronts us in patient-reported outcome (PRO) scale development and scale assessment. One model does not fit all data or scale types, which can have serious ramifications for researchers dependent on good scales. By applying the wrong model, scales can be improperly assessed and erroneously dismissed, wasting research time and dollars.

In scale development, the reflective indicator model (RIM) underlies most scaling methodologies, from coefficient alpha to factor analysis and item response theory (IRT)/ Rasch modeling. The RIM treats the observed variables as reflections of underlying latent variables or true scores. Unfortunately, this model is indiscriminately applied to many datasets given its dominance. Given the methods that have been developed, early scaling methodologists clearly must have dealt primarily with the type of data best served by this model. One sees little reference to alternative models in much of the classical literature, leading Bollen[1] to make the startling note that the first systematic discussion of model selection occurred relatively late in a 1971 paper by Blalock.[2]

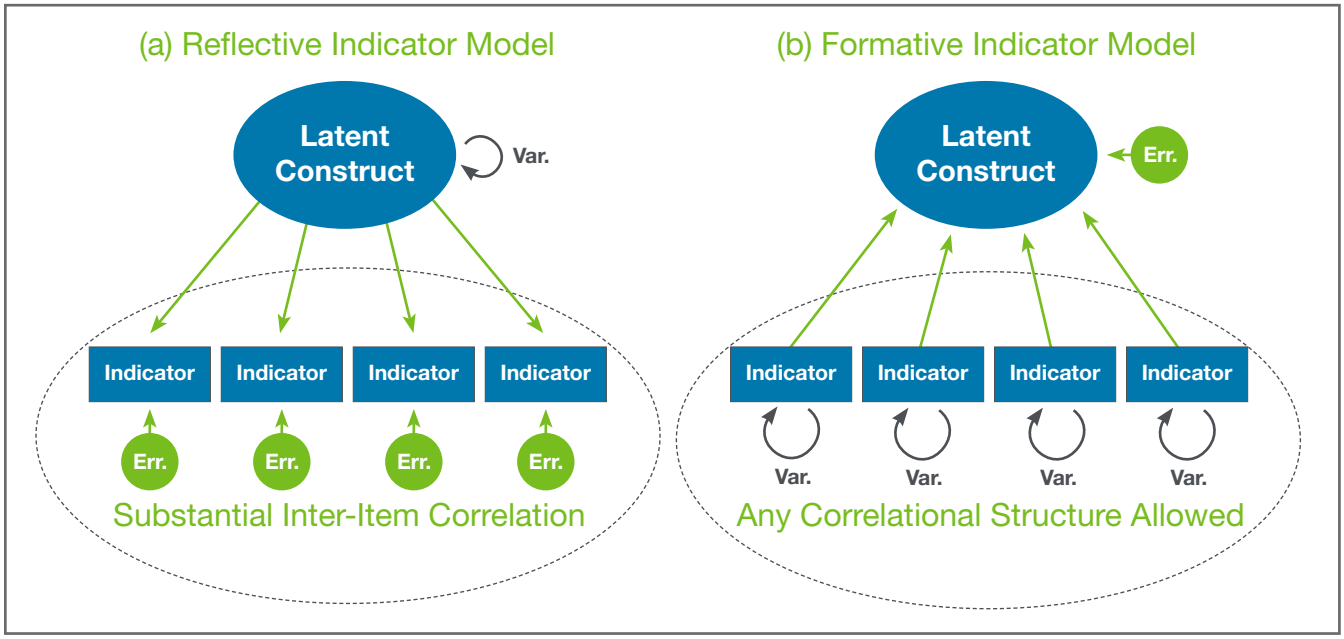
Today, in the face of an explosion of scale creation, methodologists are facing a greater diversity of scales as scientific measurement moves into new areas and applications. Today, methodologists are recognizing that the RIM, the cornerstone of classical and even most modern scale development, is not appropriate for some types of scale data and that alternative models and assessments need to be developed and appropriated. Recognizing the need for alternative models is important as perfectly good scales may be discarded if they do not meet expected measurement standards (e.g., coefficient alpha criteria, model fit and proper parameter estimates for factor analysis and IRT). This article will highlight one important alternative model to raise awareness of the importance of choosing the correct model for scale assessment.

To appreciate the difference between scale models, one must understand the hypothesized relationships in each model between the observed variables and the latent variable of true interest. The RIM is defined by its assumption that each indicator *reflects* the state of the latent variable, such that if that latent variable changes, every connected indicator should probabilistically "reflect" this by realizing some particular change. Of course the "reflection" may be imperfect as if by a carnival mirror because of measurement error. Another name used in the literature for such an indicator is an "effect" indicator because it shows the *effect* of the latent construct. Most of our psychometric methodologies assume there is a common source of variance for the observed variables and that this common source of variance is provided by the latent variable varying over individuals, causing correlation across individuals in the observed variables.

A less common but important alternative model to be considered, which is more appropriate for some scales, is called a formative indicator model (FIM). In this model, the causal relationship between the observed variables and the latent construct is reversed. The measured or observed variables in this case *construct* or *form* the latent variable (hence the term "formative"), which is in effect assembled from the items. Another name for this type of model is a causal indicator model because the indicator *causes* the latent construct. *Figure 1* displays a visual representation of the two models, (a) a RIM and (b) a FIM, displaying the key difference between them lying in the direction of influence of the arrows connecting the latent construct in the ovals with the four indicators, indicated by square boxes. The figure also signals a less obvious potential difference between the two, namely the degree to which there is inter-item correlation. More discussion of these two models can be found in Bollen and Lennox.[3] The FIM is also discussed in detail in Bollen and Bauldry[4] along with a third model not presented here.

Before discussing the problems with applying typical psychometric methods to FIM scales, a few examples are in order. A commonly encountered example of an FIM scale type is the typical stress scale, in which a list of stressors

Figure 1: Two different models underlying the most commonly used scales



is presented and the respondent indicates whether that particular stress-inducing event has occurred in that person's life during the stated period of time. The guiding theory posits that occurrence of such events would likely raise that person's stress level. What is important to note with this stress scale example is the relationship between the variable of interest, the person's stress level, and the observed variables, the individual stressors. The occurrence of the observed stressor has a causal effect on the unobserved stress level. The reverse, a manipulation of the stress level, would not cause the occurrence of each of the stressful events.

Another example might be a social engagement scale. Here individual items, time spent with family, time spent with friends, time spent with work colleagues, etc., together constitute an overall social engagement, but each bundle of engagement time builds separately on the others to form the overall engagement variable. It does not make sense to vary the overall social engagement without deterministically (not probabilistically) varying at least one of the individual components. However, there may be another latent variable, say a latent sociability variable that could drive each of those parts. This example highlights the fact that carefully thinking about the latent variable and any causal direction vis-à-vis observed variables is crucial, as the same set of observed variables can represent two different latent variables depending on how they are modeled. While an individual sociability characteristic or trait may be related to a social engagement construct, they are clearly not the same variable.

A third example, seen in the outcomes research field may be in the assessment of symptoms. Such assessments may be used in a symptom impact index, designed to measure the cumulative impact of the person's symptom experience on his or her health-related quality of life. In this example, the best model is an FIM, as the symptom experiences add up to and are causal of an overall symptom impact. An alternative use of symptom indices occurs in measures of disease severity, wherein symptom expression is an indicator of how severe the person's disease state is. For this use, the RIM is appropriate as the observed symptoms are seen as reflective of the underlying disease severity. Again, as in the previous example, depending on the causal direction assumed in the measurement model used, the same set of observed variables may be used for two different latent variables. Sometimes more refined measurement is obtained by using item wording that focuses respondent attention to symptom *impact* on health-related quality of life, so the question is not just about the presence of the symptom, but about the degree to which its presence is having an impact on daily life.

A corollary of the causal direction embedded in each model is the correlational structure and item independence. In the RIM, a change in one observed variable should be accompanied by changes in all the variables as the implication of the model is that the latent variable must have changed with the observed variable since it is but a reflection of the latent variable. In the FIM, any observed variable can change independently, not necessitating a correlated change in any other observed variable per the model. The degree of correlation among the observed variables in the FIM can vary from high to none at all.

The complete lack of any specification of inter-item correlation among the observed indicators in the FIM is the reason why FIM scales may, on occasion, meet good scale criteria, but more often will fail to meet such criteria; this is where researchers can encounter difficulties in their scale development if they use the wrong model. In RIM scales, there is a strong basis for correlation among the indicators because all of them share a common cause.

In contrast, the FIM scale contains no common cause of the indicators, so there is nothing in the model that specifies any necessary degree of correlation. Completely uncorrelated items may still form a very good formative index. For example, in a stress index, the two items, (a) being the victim of an automobile accident and (b) having a close family member who is terminally ill, may have virtually no correlation. There is no model assumption that raises the likelihood of both circumstances happening at the same time. Components of scale analysis that assume a common correlation among all the indicators, and test for or assess it, are quite appropriate for the RIM, but not appropriate for the FIM. Coefficient alpha assesses common inter-item correlation. Factor analysis estimates parameters around an assumed common cause of observed variable correlation. (*Figure 1*a is the classic graphical presentation of the basic factor analysis model.) Similarly with a slightly different model, IRT and Rasch models are built around a common source (the latent trait) of item correlation (response propensity).

When these scale analysis methods are applied to formative scales they occasionally will, but more likely will not, meet certain required criteria. It all depends on how much correlation exists among the formative indicators, either from other common causes some of the items may share or due to causal relationships among the indicators themselves. When formative scale items do show considerable correlation and the typical psychometric analysis is used with this data, this correlation may mask FIM items as RIM items, wrongly attributing that observed inter-item correlation to a latent construct, which is assumed under RIM to be a "causal" agent. The unfortunate consequence is that when formative items are tested with reflective model tests, they either (1) provide deceptive information in the form of parameter estimates for a completely miss-specified model, or (2) when inter-item correlation is low or non-existent (which is entirely acceptable in the formative scale), they may fail to meet the required levels of correlation and be inappropriately discarded. For further information regarding formative scales and their assessment, see Bollen and Ting,[5,6] Hipp et al.,[7] and MacCallum and Browne.[8]

WHEN INAPPROPRIATE MODEL ASSUMPTIONS ARE APPLIED, PROBLEMS WILL BE ENCOUNTERED AND RESEARCHERS WILL BE PLAGUED BY PUZZLING AND INCONSISTENT RESULTS.

It is a very real possibility that researchers today may encounter and need to assess such scales. (Some may even have a mix of reflective and formative indicators.) By starting with an awareness of this issue and thus being able to make appropriate model choices, scale analysis can proceed in a sensible way. When inappropriate model assumptions are applied, problems will be encountered and researchers will be plagued by puzzling and inconsistent results.

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Proceed Boldly Yet Cautiously — Psychometrics in the Patient-reported Outcomes (PRO) World

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INTRODUCTION

Advanced psychometric techniques have been gaining ground in recent years in evaluation of patient-reported outcome (PRO) instruments.[1,2] Properly applied, psychometric modeling (whether from the IRT or Rasch families) can provide unparalleled power in detecting non-functioning items, help define disease-specific outcomes and specify responder behavior. Misused, these methods can lead to wrong inferences about the population and the selection of inappropriate items for analysis.

The advantages parametric modeling provides to instrument development and population behavior are reviewed here, together with words of caution regarding indiscriminate application of the measurement theory models.

PROCEED BOLDLY!

Item response theory (IRT) defines patient responses to each individual item as a function of the patient's characteristic (latent trait) and the characteristics of the item (generally called discrimination and difficulty following educational measurement conventions). IRT is a powerful technique allowing for more in-depth understanding of the underlying population and item characteristics.

Because IRT has been used extensively in educational testing over the last 40 years, robust analytic techniques have been developed for most of the estimation problems. Unlike the Classical Test Theory techniques that describe patient performance in terms of domain or total score, considering all items to be equal, the IRT approach examines each item's contribution to the construct measured by the whole instrument. With IRT, given acceptable item fit, more information can be gleaned about the quality of measurement and, because person latent traits and item difficulties are on the same scale, an immediate check of whether these two are compatible is possible. In particular, the following issues have strong theoretical underpinnings:

1. **Construction of new instruments with strong measurement properties;**
2. **Evaluation of the fit of each individual item to the measurement model chosen;**
3. **Evaluation of the statistical consequences of choosing some items over others for the instrument;**
4. **Evaluation of the relative merits of different instruments measuring the same trait;**
5. **Detection of the presence of potentially biased items; and**
6. **Detection of changes in latent trait across different evaluation times for subpopulations of interest.**

IRT methods allow for collecting items measuring the same latent trait for building robust and statistically valid item banks. In addition, they naturally provide a measurable degree of precision at every latent trait and, through item and test information, describe the degree of precision of both the individual item and the whole instrument at each level of latent

PROPERLY APPLIED, PSYCHOMETRIC MODELING (WHETHER FROM THE IRT OR RASCH FAMILIES) CAN PROVIDE UNPARALLELED POWER IN DETECTING NON-FUNCTIONING ITEMS, HELP DEFINE DISEASE-SPECIFIC OUTCOMES AND SPECIFY RESPONDER BEHAVIOR.

trait. This is paramount in developing parallel forms of instruments, what is especially salient in Computer Adaptive Testing where in-depth information about each item is necessary in order to pick the one most appropriate to the current estimate of the latent trait of the patient. Applying IRT techniques can also be useful at the development stage of the instrument when psychometric item fit and distractor performance can be examined in order to select items that best fit the population.

Additional techniques readily available when using psychometrics are Differential Item Functioning (DIF) and equating. Differential Item Functioning was developed as part of Classical Test Theory and then expanded by application of IRT methods. DIF helps to identify potentially biased items, i.e., items for which one subgroup (for example, males when DIF due to gender is being examined) scores differently (lower or higher) on the item than the other subgroup when controlled for the latent trait. As the population can be partitioned in many ways (for example, by gender, race, education, disease group division), this is a very powerful technique alerting the researcher to problems with certain items, but more importantly, having the potential to further inform the instrument development process. Thus, DIF is quite useful in PRO development to examine for subgroup differences in responses for particularly heterogeneous patient populations, but also to provide quantitative measure of variabilities discovered during the qualitative phase of development (provided adequate sample is available).

Equating allows for patient latent traits (i.e., scores) obtained across different administrations of the instrument to be put on the same scale. In particular, while the follow-up version of an instrument might differ from the baseline version (through, for instance, the addition of new items), as long as the number of overlapping items is sufficient (30 to 70 percent, depending on the construct[3]), the IRT-based scale score from the two instruments can be directly compared with equating. This in turn allows for valid interpretations of any observed improvements in score. Another application of equating scale scores would be equating two different populations (e.g., the pediatric and adult cancer patients) so that they can also be directly compared.

PROCEED CAUTIOUSLY!

While software for analysis of instrument responses has been developed (e.g., RUMM, IRTPRO, Multilog, and even an experimental SAS procedure), both the setting up of the models and the interpretation of the output are not always as straightforward as they might seem and should be approached with care. In particular, standard normal distributions for the latent trait and the difficulty parameter are generally assumed and will be generally estimated; however, if this is not the case with the PRO (if, for example, the behavior is unipolar, like alcohol abuse disorder, or bimodal, like spinal muscular atrophy) care should be taken to set reasonable initial estimates of population statistics.

One should never forget that item response theory models come with strong parametric assumptions; all models have the assumption of unidimensionality (only one trait is measured by a collection of items), monotonicity (probability of a higher response increases with increased latent trait) and local independence (only the latent trait explains the performance on the item conditioned on it; the

responses are independent). While small deviations from the three assumptions are permissible[4,5], conspicuous violations of any of these assumptions result in faulty inferences about model fit and the violation of construct validity (i.e., what is measured by the instrument is no longer what was intended, and may, in fact, be impossible to ascertain). In the context of PRO instruments, this directly translates into the impossibility of interpretation of the significance of improvements in the score. If violations are suspected, either IRT is not appropriate for the scale or more advanced IRT approaches need to be employed (such as ones developed by Mark Reckase[6] or Howard Wainer[7]).

Furthermore, a much larger sample size than for nonparametric analysis is needed in order to provide reliable estimates of thresholds. While the recommendation of the sample sizes varies[8,9] and has not been systematically studied in the high-reliability PRO realm, generally, at least 300 patients per item is recommended.[10] However, some authors[11] indicate that sample sizes exceeding 100 are sufficient for Rasch modeling of PRO data, while others[12] point to the number of items and variances of scores as being more consequential for estimation.

The Food and Drug Administration (FDA) encourages, but does not require, the use of IRT or Rasch analysis as part of the PRO instrument development and evaluation process for those PRO endpoints that will be used for product labeling.[13] To the best of our knowledge, these psychometric analyses have generally resulted in more focused conversations and in the development of instruments more grounded in measurement theory. However, misusing the IRT or Rasch analysis can lead to inappropriate inferences about both the items and the population of interest, especially if the local independence, unidimensionality and monotonicity assumptions are violated.

The Rasch-only approach to instrument analysis does have an immediately observable disadvantage. Because the same discrimination parameter is assumed and estimated for all items, item dependencies might not be immediately apparent, especially if residuals and residual correlations are not examined carefully. In more parameter-heavy models, item dependencies can be immediately assessed by unusual behavior of each item's discrimination parameter. In fact, the validity assumption of the same value of the discrimination parameter for every item should be carefully considered. As it is presumably somewhat impossible to ascertain the validity of this assumption from the content perspective, it is probably safer to check if discriminations are similar in the Generalized Partial Credit Model and the Graded Response Model.

Despite all the above caveats regarding the Rasch model, it needs to be stated that if the Partial Credit Model fit is found to be comparable to any other psychometric model, it should be favored over other models because of its simplicity and relative ease of interpretation of output.

CONCLUSIONS

We are by no means claiming that this is a complete list of advantages of IRT and warnings about misapplying the models. We are hoping, however, that this article will give the reader both insight and pause about this exciting direction that PRO research has been taking over the last 10 years.

It is true that careful application of psychometric techniques will greatly inform the instrument development process and provide incredible insight into patient responses as a function of their disease severity. The blind application of these techniques, however, could result in faulty inferences and thus substantive misjudgments in the validity of the resulting instrument, and therefore potentially fatal conclusions regarding the trait measured and improvements in score.

We cannot stress enough that the presence of reliable estimates

for psychometric methods is not a guarantee of either content or construct validity of the instrument and will not compensate for failures in data collection, item phrasing, population misspecifications, etc.

The validity of instrument development still needs to hold, and methods to ensure this validity have been discussed in this forum before.[14,15]

A careful examination of the data and its assumptions will ensure success with applying any model and lead to reliable and valid conclusions, resulting in a more powerful instrument being developed.

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The Probability of a Successful Probabilistic Sensitivity Analysis

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INTRODUCTION

Probabilistic sensitivity analysis (PSA) is increasingly viewed as a required step in conducting economic evaluations[1] and a formal requirement from agencies such as the National Institute of Health and Care Excellence (NICE).[2] Research on the appropriate ways to structure and conduct PSA and to present results has been prominent in health economics in the last decade[3,4] with a best practices guideline published in 2012 by the joint International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and Society for Medical Decision Making (SMDM) Task Force.[5]

Among other recommendations, the ISPOR-SMDM Task Force and current and previous NICE guidelines recommend that all parameters subject to uncertainty be included in PSA; that the selection of probability distributions be based on sound statistical principles and data, avoiding arbitrary measures; that possible correlations among parameters be considered; and that structural uncertainty should be assessed.[2,5,6] Despite the consistency of these requirements with earlier recommendations,[7] both the implementation and the presentation of PSA in NICE technology appraisals (TAs) have received criticism.[8]

We recently conducted a review on the methods used in all completed, full (excluding patient access submissions), NICE single TAs published in 2013-2014.[9] The aim was to review the most recent approaches adopted for conducting PSA in NICE submissions, assessing whether they conform with the guidelines, if methods have improved since previous criticisms and how PSA ultimately influences decision making.

METHODS

Final appraisal documentations (FADs), evidence review groups (ERG) reports and, where available, manufacturer submissions were reviewed. Data extraction tables were designed to capture:

- The basic characteristics of the TAs
- The methods employed by manufacturers and the ERGs
- Ranges of parameters incorporated in the PSA

- Choices of probability distributions
- Sources of variation
- Assessment of structural uncertainty
- Reporting of limitations
- Overall reporting
- Influence on the ultimate decision

The PSA methods adopted were compared against the NICE reference case from the 2013 NICE guidance.[2] Data extracted by one reviewer was checked by an additional reviewer. (For further detail, please see Lanitis et al. 2014.[9])

RESULTS AND DISCUSSION

Thirty-one TAs were identified, of which 13 were excluded. Excluded TAs were: terminated (4 TAs); multiple TAs (3); revised submissions, including patient access scheme submissions (4 TAs); and lack of publicly available documentation (2). One TA was excluded for two reasons (multiple TA and lack of documents), resulting in 18 TAs included in the review.

Our findings were consistent with an earlier review that criticized the methodology and reporting used in NICE TAs prior to the 2008 and 2013 methodology guidelines.[8] We found that PSAs were heavily criticized by ERGs with at least one methodological issue reported in 84% of cases. Despite these criticisms, PSA results were considered more informative than the deterministic results in 27% of TAs. PSA results were mentioned and reviewed by the committee in almost all FAD reports (84%). However, although potentially discussed in the TA committee meetings, PSA results were only mentioned in the FADs as part of the decision in three TAs (16%).[9]

The main issues that arose from the review were the questions around the choice of distributions; the variation of input parameters; not taking into account the correlations and dependencies between the parameters; the lack of representation of structural uncertainty within PSA; and the appropriate presentation of results.

CHOICE OF DISTRIBUTION

Most TAs did not report in sufficient detail the methods used to populate the PSA and the rationale for the choice of distribution for each parameter and the variation surrounding it.[9] The choice of distribution used for parameters if justified was usually based on conventions, with no additional justification provided.

It is important for the analyst to understand the limitations of the distributions employed in comparison to the nature of the parameter varied. For example, while the gamma and lognormal distributions are bounded by 0, the upper interval of the distribution can go above 1, thus may be inappropriate when the parameter is a risk or probability and thus should be between 0 and 1. In many cases, use of a normal, gamma or lognormal distribution may still remain within the bounds of 0-1 depending on the mean and standard error; however, it is important to test this to ensure the simulated parameter falls within plausible bounds. Usually, use of the beta distribution is recommended for probabilities, as it is a conjugate of the binomial distribution.[3,7] A beta distribution can be parameterized through use of the mean and standard error; however, if the latter is not available, it can be parameterized by using the shape parameter (alpha) as the number of events observed for the preferred outcome (e.g., number of patients experiencing a given outcome) and the scale parameter (beta) as the number of failures of the outcome observed (e.g., number of patients that did not experience a given outcome).

A beta distribution may not be appropriate when the parameter modeled is a rate expressed, for example, as per 100 patient years as its natural bounds do not fall within the 0-1 range of the beta distribution. In such cases, the gamma and lognormal distribution can be considered as they are also bounded by a lower 0 limit. Caution should be exercised in utilizing the normal distribution for such parameters as estimates can go below 0. Limitations associated with the distributions should be evaluated according to each parameter varied. Several publications provide recommendations on the choice of distributions for each type of parameter.[3,5,7]

VARIATION OF INPUT PARAMETERS

In the reviewed TAs, the variation for the parameters was in most cases assumed and not informed by data, with 68% of TAs including at least one parameter where the standard error was assumed to be 10–30% of the mean, with 20% being the most common assumption.[10] In some TAs, the assumed variation was large and extensive, e.g., varying all parameters by 30%, while in others it was minimal and applied only to selected costs. No justification was reported for the size and extent of this variation.

Arbitrary variation of parameters, however, leads to arbitrary results and misrepresentation of the uncertainty. A scatter-plot or cost-effectiveness acceptability curve (CEAC) plotted assuming 20% variation in all parameters may over- or under-estimate uncertainty surrounding the decision. It does not, as intended, reflect the uncertainty of the results and the decision due to parameter uncertainty, but on arbitrary assumptions of uncertainty. Recently developed models tend to have a large number of parameters, and the assessment of uncertainty surrounding them is difficult. In most

cases, however, 95% confidence intervals, standard errors, minimum and maximum, patient numbers or patient-level data are available to inform estimates of variation. Where nothing is available, transparency is required from the analyst regarding the choice of variation, with explicit acknowledgement of the limitations of the analysis.

CORRELATIONS AND DEPENDENCIES AMONG INPUT PARAMETERS

Although guidelines suggest the incorporation of correlation and dependencies between parameters, only one of the 18 reviewed TAs considered this.[9] This is a major limitation in most PSAs as correlation and major dependencies between parameters exist in almost all models. One example is the progression-free survival and overall survival in oncology models. A patient can't progress after they have died, yet independent variation of the survival curves could lead to these curves crossing. In addition, these curves are often varied independently of the comparator curves incorporating the implicit assumption of no correlation between comparators. The assumption of no correlation in these cases can lead to misleading probabilistic results and the overestimation of uncertainty.

Similarly, various other input parameters in a model can be correlated. For example, independent variation of parameters could lead to assigning higher utility values to milder conditions than to more severe conditions in some simulations. Parameters can be correlated using the Cholesky decomposition[7] and methodologies have been proposed to address dependencies such as using z scores to maintain continuity between parameters.[10] The analyst should consider the presence of correlation or dependencies in the model and evaluate their potential influence on the results. If such aspects are not considered in the PSA, appropriate caveats and limitations need to be presented alongside results, including potential scenario analysis of the PSA to gain an understanding of where the true probabilistic estimates may lie.

PRESENTATION OF RESULTS

Several TAs reported mean incremental cost-effectiveness ratios (ICERs) and confidence intervals surrounding the ICER. However, as the ICER is the ratio of the incremental costs and the incremental health benefits, a negative ICER can suggest that the new health technology is less costly (has negative incremental cost) and more effective (has positive incremental health benefit) or it can suggest that the new health technology is more costly (has positive incremental cost) and less effective (has negative incremental health benefit). Similarly, the positive ICER can have opposing interpretations.

Due to this inherent complexity of the ICER having alternative interpretations when falling in different quadrants of the scatterplot,[7] the calculation of confidence or credible intervals around the ICER is not straightforward and there is no consensus on the appropriate methodology. Various methods have been proposed and challenged.[11] Due to these limitations, the scatter-plots and cost-effectiveness acceptability curves can be a more appropriate way of representing uncertainty around the ICER than confidence or credible intervals when observations fall in more than one quadrant.[5,12] It is important for the analyst to understand these limitations before presenting confidence or credible intervals.

ERGs often require reporting of a mean probabilistic ICER. In this case, the abovementioned limitations of the ICER need to be assessed as well. The mean probabilistic ICER can also differ from deterministic results and, if this is the case, it is important to understand the source of the deviation. Recording the values that each parameter takes in the individual simulations together with the results and analyzing the recorded data using regression techniques can prove to be a useful tool in understanding results and drivers of this discrepancy and potential non-linearities. A careful consideration of the number of simulations included in the PSA could also provide solutions. In the reviewed TAs, the median number of simulations used for the PSA was 1,000, varying between 1,000–10,000. However, only one TA provided a rationale for the number of simulations.[9] A formal test of convergence[13] can aid the choice in the appropriate number of simulations required.

CONCLUSION

Compared to the previously conducted review,[8] there seems to be insufficient improvement in conducting PSAs for TAs, with the majority of TAs still not conforming to best practices. Consequently, the interpretation of the probabilistic results is limited by the use of arbitrary variation, methodological

inaccuracies, insufficient reporting and various implicit assumptions as well as the omission of uncertainty in key parameters. As a result, there is a danger that the probabilistic results better represent the underlying assumptions of the analyst than the true impact of parameter uncertainty and can therefore be misleading when informing decision making.

There is considerable scope for improvement when conducting and interpreting PSAs, while the various aspects and challenges in methodology require further research and discussion. In addition, due to these various challenges, the analysts should fully and transparently report on the assumptions required and the limitations of the approaches taken so that they may be taken into account in the decision making.

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Evidera Presents at ISPOR's 17th Annual European Congress

8 – 12 November 2014 • Amsterdam, The Netherlands

SHORT COURSES

MORNING - Sun., 9 Nov
08:00 – 12:00

Discrete Event Simulation for Economic Analyses – Concepts

INSTRUCTORS: J. Jaime Caro, MDCM, FRCPC, FACP, Chief Scientist, Evidera; **Jorgen Moller,** MSc Mech Eng, VP, Modeling Technologies, Evidera; **Ipek Ozer Stillman,** MSc, Sr. Research Scientist, Modeling & Simulation, Evidera

AFTERNOON - Sun., 9 Nov
13:00 – 17:00

Discrete Event Simulation for Economic Analyses – Applications

INSTRUCTORS: J. Jaime Caro, MDCM, FRCPC, FACP, Chief Scientist, Evidera; **Jorgen Moller,** MSc Mech Eng, VP, Modeling Technologies, Evidera; **Ipek Ozer Stillman,** MSc, Sr. Research Scientist, Modeling & Simulation, Evidera

ISPOR FORUM

SESSION I – Mon., 10 Nov
18:00 – 19:00

An Introduction to Multi-criteria Decision Analysis in Health Care Decision Making - Emerging Good Practices

MODERATOR: Maarten J. IJzerman, PhD, Prof. Health Technology & Svcs. Research, MIRA Institute for Biomedical Technology, Univ. of Twente

SPEAKERS: Nancy Devlin, PhD, Research Dir., Office of Health Economics; Praveen Thokala, PhD, Research Fellow, School of Health and Related Research, Univ. of Sheffield; **Kevin Marsh,** PhD, Sr. Research Scientist and Dir., Modeling & Simulation, Evidera

WORKSHOPS

SESSION III – Tues., 11 Nov
16:45 – 17:45

W14: The Ethical and Legal Issues Around the Use of Social Media to Get to the "Real World"

DISCUSSION LEADERS: Andrew Cox, PhD, Research Scientist, Retrospective Observational Studies, Evidera; H. Keri Yang, PhD, Dir., Global Health Outcomes, Merck & Co.; Ruth Suter, MBA, Sr. Dir., Market Access and Patient Svcs., BioMarin Pharmaceuticals

SESSION IV – Wed., 12 Nov
08:45 – 09:45

W21: Patient Engagement in Outcomes Research: Current Status, Questions, Beliefs, and Future Perspectives

DISCUSSION LEADERS: Rachel Harrington, BA, Assoc. Regulatory Affairs Mgr., Astellas Pharma; **Asha Hareendran,** PhD, Sr. Research Leader, Evidera; Todd Berner, MD, Dir., HE and Clinical OR, Astellas Scientific and Medical Affairs; Amie M. Scott, MPH, Research Project Mgr., Memorial Sloan Kettering Cancer Center

SESSION V – Wed., 12 Nov
13:45 – 14:45

W26: How an Early Network Meta-analysis (NMA) Helps Inform Clinical Trials Design and Technology Appraisal (TA) Submissions

DISCUSSION LEADERS: Yingxin Xu, PharmD, PhD, Research Scientist, Meta Research, Evidera; **Kyle Fahrbach,** PhD, Sr. Biostatistician, Meta Research, Evidera; Floortje E. van Nooten, MSc, Assoc. Dir., HEOR, Astellas; Grace Jennings, PhD, Technical Adviser, National Institute for Health and Care Excellence (NICE)

SESSION VI – Wed., 12 Nov
15:00 – 16:00

W29: Supporting Decision Making with MCDA: Recommendations for Dealing with Uncertainty

DISCUSSION LEADERS: Maarten J. IJzerman, PhD, Prof. Health Technology & Svcs. Research, MIRA Institute for Biomedical Technology, Univ. of Twente; Henk Broekhuizen, MSc, Health Technology & Svcs. Research, Univ. of Twente; Karin Groothuis-Oudshoorn, PhD, Asst. Prof. Health Technology & Svcs. Research, Univ. of Twente; **Kevin Marsh,** PhD, Sr. Research Scientist and Dir., Modeling & Simulation, Evidera

RESEARCH PODIUM PRESENTATION

SESSION I – Mon., 10 Nov
14:15 – 15:15

QA2: Cost-Utility of Cancer Therapies - the "Cost" of Different Utility Generation Strategies

Meads DM, McCabe C, Hulme CT, Edlin R, Kharroubi SA, **Browne C,** Ford H, Dunn J, Marshall A

POSTER PRESENTATIONS

SESSION I – Mon., 10 Nov
08:45 – 14:15

PND4: A Comprehensive Literature Review of the Burden of Gaucher Disease

Nalysnyk L, Hamed A, Hurwitz G, **Simeone J, Rotella P**

PND47: Comparison of a Markov Cohort Model and a Discrete-Event Simulation for Economic Analyses of Treatments for Multiple Sclerosis

Kansal A, Tafazzoli A, Leipold R, Sarda S

PGI13: Direct Health Care Costs Associated with Opioid-induced Constipation

Lawson R, **Haycock L, Laxman K,** King F, **Gardner K**

PMS26: Economic Modeling of the Use of Botulinum Toxin A in a Homogenous Patient Population Based on Real-Life Clinical Practice: ULIS-II (The Upper Limb International Spasticity Study)

Dinet J, **Lambrelli D,** Balcaitiene J

PDB128: German Patients' Preferences for Attributes of Type 2 Diabetes Medications

Gelhorn H, Stringer SM, Reinders S, Schreeb K

PGI36: How Does Non-Malignant Opioid Induced Constipation (OIC) Impact Health State Utility?

Lawson R, **Marsh K, Altincatal A,** King F

PDB136: Psychometric Evaluation of the Hypoglycaemia Perspectives Questionnaire in Patients with Type 2 Diabetes Mellitus

Ong SH, **Kawata AK,** Kulich K, **Wilson H, Coyne KS,** Evripidou P, Koutsides P, Kyriakidou-Himonas M, Loizou T, Olympios G, Pastellas C, Picolos M, Stylianou A, Toufexis C, Therapontos C

PMS75: Qualitative Equivalence between a Paper and Electronic Tablet Version of the WOMAC ® NRS3.1 and Patient Global Assessment

Eremenco S, Fleming S, Riordan D, **Stringer S, Gleeson S,** Sanga P, Kelly K

PMS77: Usability Testing of a Novel Pain Medication Diary Administered Electronically

Eremenco S, Fleming S, Riordan D, **Stringer S, Gleeson S,** Sanga P, Kelly K

SESSION II – Mon., 10 Nov 15:30 – 19:30

PHP177: Legal and Ethical Implications of Using Data from Social Media Websites

Khankhel Z, Abogunrin S, Martin A

SESSION III – Tues., 11 Nov 08:45 – 13:30

PSY90: A Systematic Literature Review of the Humanistic Burden of Multiple Myeloma

Rizzo M, Xu Y, Panjabi S, **Iheanacho I**

PCV119: Acute and Chronic Impact of Cardiovascular Events on Health State Utilities

Matza LS, Devine MK, Gandra SR, Delio PR, Fenster BE, **Davies EW, Jordan J,** Lothgren M, Feeny DH

PCV90: Cost-Effectiveness of Apixaban Compared to Other Anticoagulants for Lifetime Treatment and Prevention of Recurrent Venous Thromboembolism

Lanitis T, Hamilton M, Rublee DA, **Leipold R, Quon P, Browne C,** Cohen AT

PCV107: Cost-effectiveness of LDL-P-Guided Statin Therapy

Folse H, Rengarajan B, Goswami D, Budoff M, Kahn R

PCV153: Dabigatran Users with Non-Valvular Atrial Fibrillation in the US: A Characterization of Dabigatran Initiators and Switchers

Shash D, Schnee J, **Schneider G,** Schoof N, Zint K, Clemens A, Bartels DB

PCV14: Lifetime Clinical Events Avoided and Resource Utilization with Apixaban Compared to Low-Molecular-Weight Heparin Followed by a Vitamin K Antagonist for the Treatment and Prevention of Venous Thromboembolism

Hamilton M, Phatak H, **Lanitis T,** Mardekian J, Rublee DA, **Leipold R, Quon P, Browne C,** Cohen AT

PIH99: Patient Characteristics and Medication Treatment Patterns among Men with Erectile Dysfunction (ED), Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia (BPH-LUTS), or Co-Occurring ED and BPH-LUTS in the UK Primary Care Setting

Ilo D, **Raluy-Callado M,** Graham-Clarke P, **Donaldson R,** Birt J, **Sadasivan R,** Zhu Y, **Neasham D**

PSY35: Pill Burden, Healthcare Resource Utilization and Costs among Subpopulations of Immediate Release Hydrocodone Users

Ben-Joseph R, Yang S, **Yang E,** Holly P, **Boulanger L**

PSY37: Rates of Diagnosed Opioid Abuse or Dependence and Incremental Direct Healthcare Costs among Patients with Long-term Use of Immediate Release Hydrocodone

Ben-Joseph R, **Yang E, Huse S, Bhagnani T,** Holly P, **Kansal A**

PSY111: Self Reported Healthcare Resource Use and Indirect Economic Burden of Opioid Induced Constipation (OIC)

Alemayehu B, **Coyne KS,** King F

SESSION IV – TUES., 11 Nov 15:30 – 19:30

PRS73: A Comparison of the Reliability and Validity of the Four-Item and Six-Item NISCI Symptom Summary Scores

Mocarski M, **Trundell D, Zaiser E,** Garcia Gil E, Lamarca R, **Hareendran A**

PRM47: A De-Novo Economic Model to Assess Clinical and Economic Consequences of Bronchiectasis

Bhattacharyya SB, Calado F, Priedane E, Shirore RM, Haworth CS, Flume PA, Sonathi V, Thomas SK

PRM230: A Statistical Modeling Framework to Characterize the Impact of Progression on Survival in Oncology

Ishak KJ

PRS26: An Analysis of US Medicare Beneficiaries: Burden of Direct Medical Costs in Patients with Idiopathic Pulmonary Fibrosis

Chen S, Collard HR, Yeh W, Li Q, Lee Y, **Wang A,** Raghu G

PRM253: An Epidemiologic Modeling Application to Pharmacoeconomics for Improved Healthcare Planning

Cid Ruzafa J, Cox A, Merinopoulou E, Baggaley R, **Leighton P, Desai K**

PRM89: Are Cycles Needed in Markov Models? - The Continuous Model as a Simpler Approach

Tichy E

PRM145: CDAD-DAYSYMS™: A New Patient-Reported Outcome Tool for Clostridium Difficile-Associated Diarrhoea

Kleinman L, Talbot GH, Schuler R, Broderick K, **Revicki D,** Nord CE

PRM243: Clinical Outcome Assessment (COA) Instrument Scoring: The Validity and Precision of Unweighted Summary Scores vs. IRT Weighted Scores, and the Added Value of IRT Standard Errors

Coon C, **Lenderking WR**

PRM73: Creating Patient Profile in Individual Simulations: A Comparison of Approaches

Stern S, Pan F

PRS11: Epidemiology and Severity of Chronic Obstructive Pulmonary Disease (COPD) in the United Kingdom (UK)

Raluy-Callado M, Lambrelli D, MacLachlan S, Merinopoulou E, Hagan MA, Khalid JM

PRM54: Estimating Means from Medians: A Case Study with Treatments for Metastatic Colorectal Cancer (MCRC)

Ozer-Stillman I, Whalen JD, Mendivil J, Villegas-Sanchez J, Chang J

PRM245: Health Technology Assessment and Environmental Costs: Time for Health Care to Catch Up?

Marsh K, Ganz M, Hsu J, Strandberg-Larsen M, Palomino Gonzalez R, Lund N

PRM125: Modelling Long-Term Changes in Opioid Induced Constipation (OIC)

Altincatal A, Lawson R, King F, **Marsh K**

PRM123: Stratified Cost-effectiveness Analysis to Guide Genetic Screening for Cancer Risk

Folse HJ, Dinh TA

PRS72: Testing e-PRO Device Usability during the Translation Process: A Case Study of the EXACT in 7 Countries

Eremenco S, Murray L

PRS71: Translation and Linguistic Validation of Two COPD Symptom Diaries (NICSI and EMSCI) for Use in 14 Countries

Eremenco S, Albuquerque P, Arnold BJ, **Trundell D, Hareendran A**

PRM75: Use of Model Averaging Techniques in Cost-effectiveness Analysis in Oncology

Le HH, Ozer-Stillman I

SESSION V – WED., 12 Nov 08:45 – 14:45

PCN81: A Systematic Literature Review of the Economic Burden in Multiple Myeloma

Rizzo M, Xu Y, Panjabi S, **Iheanacho I**

PCN14: Analysis of Treatment Options for Relapsed or Refractory Chronic Lymphocytic Leukemia (CLL)

Sallum R, Dorman E, Xu Y, Tran-Kerr K, O'Donnell M, Sorensen S, Szatkowski A, Sengupta N, Gaudig M

PCN82: Exploring the Usefulness of Social Media and Patient Forums in Identifying Indirect Costs of a Disease

Chalkiadaki C, Martin A

PCN36: Long Term Survival of Patients with Various Lung Cancer Histology in Seer between 2004-2011

Schmaus K, **Benedict A**

PCN40: Simulation Model of Ibrutinib for Chronic Lymphocytic Leukemia (CLL) with Prior Treatment

Pan F, Peng S, Sorensen S, Dorman E, Sun S, Gaudig M, Sengupta N

PCN38: Simulation Model of Ibrutinib in Treatment of Relapsed or Refractory Mantle Cell Lymphoma (MCL)

Peng S, Sorensen S, Pan F, Dorman E, Sun S, Van Sanden S, Sengupta N, Gaudig M

PCN10: Systematic Review of Relapsed or Refractory Mantle Cell Lymphoma (MCL) Clinical Trials: Implications for Decision Modeling

Sorensen S, Dorman E, Xu Y, Sallum R, Pan F, Szatkowski A, Gaudig M, Sengupta N

PCN268: The Life and Death of the End of Life Treatment Appraisal Criteria in NICE Technology Appraisals?

Kiss Z, Muszbek N, Benedict A

PCN239: What are the Healthcare Resource Utilization and Medical Cost of Untreated Patients with Neuroendocrine Tumors in the United States?

Chuang C, Dinet J, **Bhurke S,** Chen S, Gabriel S

PCN195: What Matters to Patients and Their Caregivers: Using Social Media and Patient Forums to Obtain Valuable Information from a Patient and Carer Perspective

Chalkiadaki C, Martin A

Upcoming Presentations

AAPM&R ANNUAL ASSEMBLY

Nov 13-16, 2014;
San Diego, CA, USA

ORAL PRESENTATION

Economic Modeling of the Use of Botulinum Toxin A in a Homogenous Patient Population Based on Real-life Clinical Practice: ULIS-II (The Upper Limb International Spasticity Study)

Dinet J, **Lambrelli D,** Balcaitiene J

ACR/ARHP ANNUAL SCIENTIFIC MEETING

Nov 14-19, 2014; Boston, MA, USA

POSTERS

Calibration of the Dutch-Flemish PROMIS Pain Behavior and Pain Interference Item Banks in Patients with Chronic Pain

Crins MHP, Terwee CB, Smits N, de Vries A, de Vet HCW, Dekker J, Westhovens R, Cella D, Cook K, **Revicki D,** van Leeuwen J, Boers M, Roorda LD

Calibration of the Dutch-Flemish PROMIS Physical Functioning Item Bank in Patients with Chronic Pain

Crins MHP, Roorda LD, de Vries A, Smits N, de Vet HCW, Westhovens R, Cella D, Cook K, **Revicki D,** van Leeuwen J, Boers M, Dekker J, Terwee CB

AHA AMERICAN HEART ASSOCIATION SCIENTIFIC SESSIONS

Nov 15-19, 2014; Chicago, IL, USA

POSTER

Re-hospitalization Rates Following Stroke and Major Bleeding in Nonvalvular Atrial Fibrillation Patients

Naccarelli G, **Stokes M, Wang R,** Deleon A, Tate N, **Wang A,** Fredell J

ASH 56TH ANNUAL MEETING AND EXPOSITION

Dec 6-9, 2014;
San Francisco, CA, USA

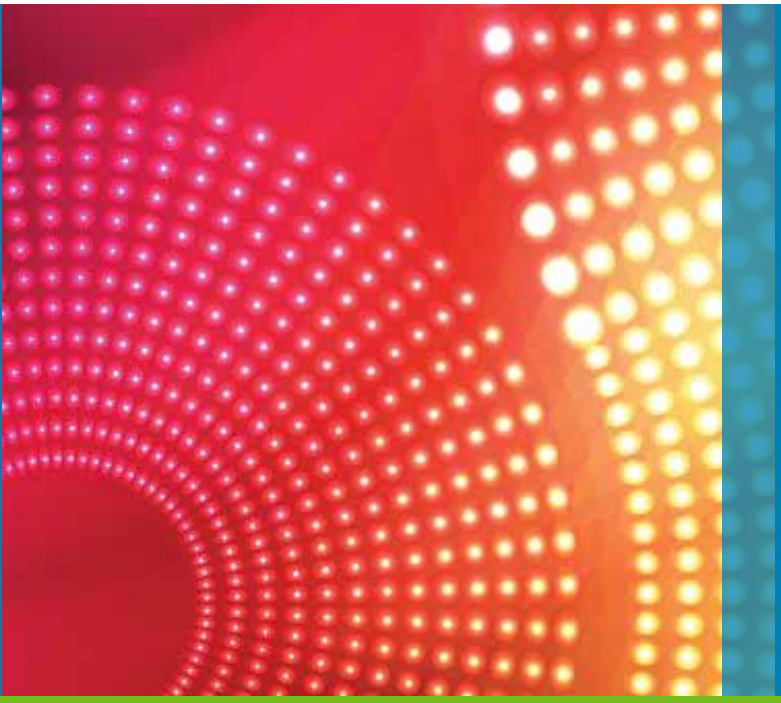
POSTERS

Cost-effectiveness Analysis (CEA) of Sequential Treatment with Tyrosine Kinase Inhibitors (TKIs) for Chronic Myelogenous Leukemia (CML)

Whalen J, Stillman I, Ambavane A, Felber E, Makenbaeva D, Bolinder B

Epidemiology and Clinical Characteristics of Patients with Multiple Myeloma in the United Kingdom

Raluy M, Ramagopalan S, Panjabi S, **Lambrelli D**



COMPLIMENTARY WEBINAR

Market Access for Orphan Drugs in China

Tuesday, November 18, 2014, 10:00 AM EST

EVIDERA PRESENTERS: Susanne Michel, MD, European Practice Lead, Payer Strategy, Evidera; Xia Chen, PhD, Consultant, Payer Strategy, Evidera

For more information on this webinar and other webinar topics, visit www.evidera.com/webinars.

Recent Presentations

ICPE 2014

Oct 24-27, 2014; Taipei, Taiwan

POSTER

Predictive Analysis for Identifying Post Stroke Spasticity Patients in UK Primary Care Data

Cox A, Raluy M, Gabriel S, **Wang M,** Bakheit A, Moore AP, Dinet J

UEG UNITED EUROPEAN GASTROENTEROLOGY WEEK

Oct 18-22, 2014; Vienna, Austria

POSTERS

Psychometric Evaluation of the Coping, Daily Life Impact, and Emotional Impact Modules of the Ulcerative Colitis Patient-Reported Outcomes (UC-PRO) Measure

Higgins PD, **Harding G**, Patrick DL, **Revicki D**, Chen WH, Globe G, Viswanathan HN, Fitzgerald K, Trease S, Borie D, Ortmeier BG, **Leidy NK**

Psychometric Evaluation of the Signs and Symptoms Modules of the Ulcerative Colitis Patient-Reported Outcomes Measure (UC-PRO/SS)

Higgins PD, **Harding G,** Patrick DL, **Revicki D,** Chen WH, Globe G, Viswanathan HN, Fitzgerald K, Trease S, Borie D, Ortmeier GB, **Leidy NK**

EAPS 2014

Oct 17-21, 2014; Barcelona, Spain

POSTER

The Economic Impact of Low Protein Formula for the Children of Overweight and Obese Mothers

Marsh K, Orfanos P, **Moller J,** Revankar N, Detzel P, Grathwohl D

ISOQOL 21ST ANNUAL CONFERENCE

Oct 15-18, 2014; Berlin, Germany

WORKSHOPS

An Introduction to Health-Related Quality of Life Assessment

Gelhorn H, Wyrwich K

Translation Methodology for Clinical Outcome Assessments in Global Trials

Martin M, Kantzer V, **Eremenco S,** Conway K, Patrick D

SYMPOSIUM

The Case for an International PROMIS Initiative

PRESENTER: Jordi Alonso
AUTHORS: Jordi Alonso, Matthias Rose, Caroline Terwee, Sandra Nolte, **Dennis Revicki,** Chris Forrest, Dave Cella for the PROMIS International Group

POSTERS

Engaging Patients in Developing Outcome Measures - Does Context of Use Drive Methodological Decisions?

Skalicky A, Magasi S, **Hareendran A**

Experience of Pain in Patients with Moderate to Severe Plaque Psoriasis

Revicki D, Wilson H, Pinto L, Viswanathan HN

Gastroparesis Symptom Severity between Patients with Idiopathic and Diabetic Gastroparesis: Evidence for a Unidimensional Symptom Scale for Gastroparesis

Revicki DA, Camilleri M, Parkman HP

ORAL PRESENTATIONS

Developing a Conceptual Model of Patients' Experience of Migraine

Skalicky AM, Mannix S, Oko-Osi H, Widnell KL, **Hareendran A,** Corey-Lisle PK

Exploratory and Confirmatory Factor Analysis of PROMIS Pain Quality Version-2 Items

Revicki D, Chen WH, Morgan-DeWitt E, Nowinski C, Michaud K, Wolfe F, Cella D

ACCP ANNUAL MEETING

Oct 12-15, 2014; Austin, TX, USA

POSTER

Discordance between Patient and Healthcare Provider Reports of the Burden of Opioid-Induced Constipation

Datto C, LoCasale R, Payne K, **Sexton C,** Yeomans K

PHARMACCESS LEADERS FORUM

Oct 8-10, 2014; Berlin, Germany

ORAL PRESENTATION

The Balancing Act of Providing Fast Access to Breakthrough Medicines and Ensuring Evidence-based Decision-making at Market Access Level

Michel S

AMCP 2014 NEXUS

Oct 7-10, 2014; Boston, MA, USA

PODIUM PRESENTATION

Cost per Effectively Treated Patient of Biologics for Rheumatoid Arthritis in the Pharmacy Benefit Management Setting

Wu N, **Bhurke S,** Shah N, Harrison D

14TH ANNUAL BIOTECH IN EUROPE INVESTOR FORUM FOR GLOBAL PARTNERING AND INVESTMENT

Sept 30-Oct 1, 2014; Basel, Switzerland

ISSUE PANEL

When Price Gives Way to Value: Implications for Deal Making

EVIDERA PANELIST: David Alderson, MBA, EU Practice Lead, Payer Strategy, Evidera

ESMO EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY CONGRESS

Sept 26-30, 2014; Madrid, Spain

POSTER

The Cost of Survival Gains in Metastatic Colorectal Cancer (mCRC) in Four European Countries

Ozer-Stillman I, Whalen J, Ambavane A, Pietsch GA, Mohamed A, Chang J

PSYCH CONGRESS

Sept 20-23, 2014; Orlando, FL, USA

POSTER

Health-related Quality of Life in Patients with Bipolar Depression Treated with Lurasidone

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

EHMTIC EUROPEAN HEADACHE AND MIGRAINE TRUST INTERNATIONAL CONGRESS

Sept 18-21, 2014; Copenhagen, Denmark

POSTER

A Qualitative Study of the Functional Impact of Symptoms on Migraine Patients

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

DGRH (GERMAN ASSOCIATION OF RHEUMATOLOGY) CONGRESS

Sept 17-20, 2014; Dusseldorf, Germany

POSTERS

Resource Use and Cost of Patients with Rheumatoid Arthritis in Germany

Lambrelli D, Barret A, Harz S, Holzkaemper T, Karlsdotter K, Zimmermann T, Paget MA, de la Torre I, Berger R, Schubert I, Hein R

Treatment Patterns of Patients with Rheumatoid Arthritis in Germany

Lambrelli D, Barrett A, Hartz S, Holzkaemper T, Zimmermann T, Paget MA, Liu-Leage S, Berger R, Schubert I, Hein R

HEART FAILURE SOCIETY OF AMERICA 18TH ANNUAL SCIENTIFIC MEETING

Sept 14-17, 2014; Las Vegas, NV, USA

POSTER

Digoxin Toxicity: Insights from 24,547 Cases in 450 Hospitals

Hauptman PJ, Ward S, **Blume SW**

2014 JOINT ACTRIMS-ECTRIMS MEETING

Sept 10-13, 2014; Boston, MA, USA

POSTERS

Economic Burden of Multiple Sclerosis: A Systematic Review of the Literature

Ashaye AO, Cadarette S, Kinter E

Identifying an Important Change Threshold for the Multiple Sclerosis Walking Scale-12 (MSWS-12)

Mehta L, McNeill M, Hobart J, **Wyrwich K, Poon JL, Auguste P,** Zhong J, Elkins J

Multiple Sclerosis and Variation in Health Utilities: A Systematic Review of the Literature

Ashaye AO, Cadarette S, Kinter E

ORAL PRESENTATION

Co-associations of Multiple Sclerosis with Schizophrenia and Bipolar Disorder: Record Linkage Studies

Ramagopalan S, Meier U, Goldacre R, Goldacre M

ISPOR 6TH ASIA PACIFIC CONFERENCE

Sept 6-9, 2014; Beijing, China

WORKSHOPS

Development of Individual Simulation Models for HTA Submission in Asia

Zheng Y, Palencia R, **Kongnakorn T,** Cai J

The German Efficiency Frontier Approach for Economic Evaluation and the Applicability in Asia

Kamae I, **Caro JJ,** Gerber A

ICAAC 2014

Sept 5-9, 2014; Washington, DC, USA

POSTERS

A New Patient-reported Outcomes Tool for Clostridium Difficile-associated Diarrhea

Kleinman L, Talbot GH, Schuler R, Broderick K, **Revicki D,** Nord CE

Modeling the Long-term Persistence of Hepatitis A Antibody after Two-dose Vaccination Schedule in Argentinean Children

Lopez EL, Contrini MM, Mistchenko A, Kieffer A, Baggaley R, DiTanna GL, **Desai K,** Rasuli A, Armoni J

JSAPS - JAPAN SOCIETY OF AESTHETIC PLASTIC SURGERY 37TH MEETING

Sept 3-4, 2014; Tokyo, Japan

ORAL PRESENTATION

Eyelash Length and Fullness by Race, Age, and Gender: Results from a Multinational Web-based Panel Survey

Kwon O, **Kawata AK,** Bessonova L, Gallagher CJ

PAINWEEK

Sept 2-6, 2014; Las Vegas, NV, USA

POSTERS

Discordance between Patient and Healthcare Provider Reports of the Burden of Opioid-Induced Constipation during Pain Management

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

The Impact of Opioid-Induced Constipation (OIC) on Pain Management

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

ESC EUROPEAN SOCIETY OF CARDIOLOGY

Aug 30-Sept 3, 2014; Barcelona, Spain

POSTERS

Cost-effectiveness of Apixaban Compared to Edoxaban for Stroke Prevention in Non-valvular Atrial Fibrillation

Lip GYH, **Lanitis T, Kongnakorn T,** Phatak H, Liu XC, Kuznik A, Lawrence J, Dorian P

Cost-effectiveness of Apixaban Compared to Other Anticoagulants for the Acute (6-month) Treatment of Venous Thromboembolism

Lanitis T, Leipold R, Hamilton M, Rublee D, **Quon P, Browne C,** Cohen A

WACQOL - INAUGURAL MEETING

Aug 29-31, 2014; Guangzhou, China

PLENARY SESSION

Considerations in the Development of Clinician-reported Outcomes (ClinROs): Validity, Insight, Regulation and the Patient's Perspective

PRESENTER: William R. Lenderking, PhD, Sr. Research Leader, Outcomes Research, Evidera

WORKSHOP

Developing a PRO or a ClinRO for a Condition Where Patients Have Limited Insight

PRESENTER: William R. Lenderking, PhD, Sr. Research Leader, Outcomes Research, Evidera

JSM JOINT STATISTICAL MEETINGS

Aug 2-7, 2014; Boston, MA, USA

SESSION SPEAKER

Design and Analysis of Large Outcomes Trials

Schuetz A

IMCAS - INTERNATIONAL MASTER CLASS ON AGING SKIN - ANNUAL MEETING

Aug 1-3, 2014; Hong Kong, China

POSTER

Eyelash Length and Fullness by Race, Age, and Gender: Results from a Multinational Web-based Panel Survey

Kwon O, **Kawata AK,** Bessonova L, Gallagher CJ

AAIC ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE

July 12-17, 2014; Copenhagen, Denmark

POSTERS

A Prospective, Systematic Literature Review and Pooled Regression Analyses to Evaluate Brain Amyloid by Positron Emission Tomography (PET) Imaging as a Biomarker of Alzheimer's Disease (AD) Progression

Ashaye AO, Travers KU, Strand L, Di Tanna GL, Wyman BT, Booth K, Styren S, Brashear HR, Margolin R, Schmidt M, Liu E

A Prospective, Systematic Literature Review and Pooled Regression Analyses to Evaluate Cerebrospinal Fluid (CSF) Phosphorylated Tau (p-tau) and Total Tau (t-tau) as Biomarkers of Alzheimer's Disease Progression

Ashaye AO, Travers KU, Strand L, **Olsson K,** Di Tanna GL, Booth K, Styren S, Brashear HR, Streffer J, Liu E

A Prospective, Systematic Literature Review and Pooled Regression Analyses to Evaluate Global and Regional Brain Volumes by Structural MRI as Biomarkers of Alzheimer's Disease (AD) Progression

Ashaye AO, Travers KU, Strand L, **Olsson K,** Di Tanna GL, Wyman BT, Booth K, Styren S, Brashear HR, Einstein S, Novak G, Liu E

Cost-effectiveness of Memantine Extended Release for the Treatment of Moderate to Severe Alzheimer's Disease in the United States

Saint-Laurent Thibault C, Ozer Stillman I, Chen S, **Getsios D, Proskorovsky I, Hernandez L,** Dixit S

Diagnostic and Treatment Patterns and Healthcare Resource Utilization among Diagnosed Dementia Patients in the United States: A Retrospective Database Study

Yang E, Guo S, Silies H, Schauble B, **Tawah AF, Getsios D**

Expected Impact of Amyloid β Positron Emission Tomography on Diagnostic and Treatment Decisions for Suspected Alzheimer's Disease Patients

Ganz ML, Tawah AF, Chitnis AS, Silies H, Schauble B, Foster NL

ABPI PHARMACEUTICAL INDUSTRY HEALTH INFORMATION GROUP MASTERCLASS

July 10, 2014; London, UK

WORKSHOP

Delivering Real World Data Programmes to Drive Improvements in Health Outcomes

Wasiak R, Cox A, Peperell K, Percival F

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

ICE / ENDO 2014

June 21-24, 2014; Chicago, IL, USA

POSTERS

Limitations of Hypogonadism Diagnosis and Rate of Treatment in Males in the US: A Systematic Literature Review

Bodhani AR, Parker L, **Khankhel Z,** Fuldeore M, Dobs A

Reasons for Non-Treatment of Osteoporosis among Postmenopausal Patients in the United States – Patient Perspective

Papadopoulos Weaver J, **Olsson K, Sadasivan R,** Sen S

Reasons for Non-Treatment of Osteoporosis among Postmenopausal Patients in the United States – Physician Perspective

Papadopoulos Weaver J, **Sadasivan R, Olsson K,** Sen S

ECONOMICS, MODELLING AND DIABETES: THE MOUNT HOOD 2014 CHALLENGE

June 17-19, 2014; Stanford, CA, USA

WORKSHOP

Developing the Archimedes Nephropathy Model: Some Complexities and Challenges

Shum K

EULAR 2014

June 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

ICOO INTERNATIONAL CONFERENCE ON OPIOIDS

June 8-10, 2014; Boston, MA, USA

POSTER

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

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

MDS 18TH INTERNATIONAL CONGRESS OF PARKINSON'S DISEASE AND MOVEMENT DISORDERS

June 8-12, 2014; Stockholm, Sweden

POSTER

AbobotulinumtoxinA in the Management of Cervical Dystonia in the United Kingdom: A Budget Impact Analysis

Dinet J, **Desai K, Brand S, Abogunrin S,** Gabriel S, Harrower T

SMDM 15TH BIENNIAL EUROPEAN MEETING

June 8-10, 2014; Antwerp, Belgium

WORKSHOP

Incorporating Preferences into Decision Making: Selecting an Appropriate Multi-Criteria Decision Analysis Weighting Method in Health Care

MODERATOR: Kevin Marsh
SPEAKERS: Brian Reddy, Kimberly Hockley, Irina Cleemput, **Tereza Lanitis**

POSTERS

Predictors of Healthcare Costs for Cystic Fibrosis Patients in the United Kingdom

Ramagopalan S, Lambrelli D, Rubin JL, **Cox AP, MacLachlan S**

Uncertainty in Uncertainty: a Review of Probabilistic Sensitivity Analysis Conducted in Health Technology Appraisals

Lanitis T, Muszbek N, Tichy E

QCOR AMERICAN HEART ASSOCIATION

June 2-4, 2014; Baltimore, MD, USA

POSTER

Applying Clinical Trial Data to the Real-World: Apixaban, Dabigatran, and Rivaroxaban

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

HEALTH DATAPALOOZA

June 1-3, 2014; Washington, DC, USA

WORKSHOP

Forecasting the Effects of Prevention and Population Health Management Initiatives – A Workshop Using the Archimedes Healthcare Simulator (ARCHeS)

Shum K**, Thi R**

EFNS/ENS JOINT CONGRESS OF EUROPEAN NEUROLOGY

May 31-June 3, 2014; Istanbul, Turkey

POSTERS

Factors Influencing Clinically-Meaningful Physical Deterioration in Patients with Relapsing-Remitting Multiple Sclerosis: Results from the ADVANCE Study

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

Peginterferon Beta-1a Treatment Reduces the Psychological Impact of Multiple Sclerosis Relapses: Results from the ADVANCE Study

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

Study of Pseudobulbar Affect Symptoms in Veterans with Mild Traumatic Brain Injury

Fonda JR, McGlinchey RE, Milberg WP, Rudolph JL, **Hunt PR, Reynolds MW,** Yonan C

ERA-EDTA 51ST CONGRESS

May 31-June 3, 2014; Amsterdam, Netherlands

POSTER

A Systematic Literature Review of the Humanistic Burden of Anaemia Associated with Chronic Kidney Disease

Rizzo M, Iheanacho I, van Nooten FE, Goldsmith D

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, Landrian A, Boscoe A, Wandstrat T

Publications

Amin A, **Stokes M,** Makenbaeva D, Wiederkehr D, Wu N, Lawrence JH. Estimated Medical Cost Reductions Associated with Use of Novel Oral Anticoagulants vs. Warfarin in a Real-world Non-valvular Atrial Fibrillation Patient Population. *J Med Econ.* 2014 Aug 18:1-37 [Epub ahead of print]

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Clifford S, Perez-Nieves M, **Skalicky A,** Reaney M, **Coyne KS.** A Systematic Literature Review of Methodologies Used to Assess Medication Adherence in Patients with Diabetes. *Curr Med Res Opin.* 2014 Jun; 30(6):1071-1085. [Epub 2014 Feb 11]

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Company News

SYMPHONY TECHNOLOGY GROUP (EVIDERA'S PARENT COMPANY) BRINGS TOGETHER INDUSTRY LUMINARIES TO CREATE A HEALTHCARE ADVISORY COUNCIL

Evidera is excited to announce that it is part of the creation of a Healthcare Advisory Council (HCAC) comprised of experts and visionaries representing stakeholders from across healthcare. The mission of the council is to help understand the trends shaping healthcare, with a focus on the need for better and faster information, analytics, technology and insights. The council members represent all areas of healthcare, including payers, HTA agencies, non-governmental organizations, academia, patients, providers and industry. This strategic advisory council is chaired by Simon Kennedy, healthcare operations partner at Symphony Technology Group.

The first meeting occurred on October 6-7 in Washington, DC. The two-day event, titled "Delivering on the Promise of Big Data in Healthcare," brought together the members and other invited experts to discuss the path to harnessing the power of big data.

HCAC MEMBERS

RICHARD BARKER, PHD, OBE *Dir. of CASMI*
Most recently the director general of ABPI, member of the executive committee of EFPIA and council member of IFPMA. Recently published the book, "2030 – The Future of Medicine: Avoiding a Medical Meltdown."

JOHN HALAMKA, MD, MS *CIO, Beth Israel Prof. of Medicine, Harvard Chairman NEHEN, HITSP*
Chair of HIT standards panel (HITSP), cochair of the Massachusetts HIT Advisory Committee.
Practicing emergency physician.

ROBERT EPSTEIN, MD, MS *(Ret.) President, Medco-UBC (Ret.) Chief R&D Officer, Medco*
Former president of ISPOR, former member of the board of directors for DIA.

JAMIE HEYWOOD *Cofounder, Chairman, PatientsLikeMe*
Currently a chief scientist and architect for PatientsLikeMe.
Founder and past CEO of the ALS Therapy Development Institute, the world's first nonprofit biotechnology company.

ROBERT JESSE, MD, PHD *Principal Under Secretary for Health, VA*
Appointed to the board of PCORI in 2010. Received the Society of Chest Pain Center's Raymond D. Bahr Award of Excellence for contributions to improving emergency cardiac care.

JENS GRUEGER, PHD *VP, Head of Global Pricing & Market Access, Roche*
Currently he and his team are responsible for demonstrating and capturing the value of Roche's product portfolio so that patients have fast and broad access.
Former executive at Pfizer and Novartis, former director of ISPOR.

PETER KOLOMINSKY-RABAS, MD, MBA *(Retired) Dir., IQWiG*
First director of health economics for IQWiG.
Founded Erlangen, one of the largest stroke registries in the world. Currently directs ProHTA, a consortium of academia and industry to advance health technology assessment.

Company News

KATHY WYRWICH NAMED TO HEAD EVIDERA'S CENTER OF EXCELLENCE IN OUTCOMES RESEARCH

KATHLEEN (KATHY) W. WYRWICH, PHD
Executive Director of Evidera's Center of Excellence – Outcomes Research.

Kathleen (Kathy) W. Wyrwich, PhD, a senior research leader at Evidera, has been appointed as the executive director of Evidera's Center of Excellence in outcomes research. Kathy has more than 15 years of experience in the field, with leadership positions in both academia and consulting.

Evidera's Centers of Excellence were established to ensure we remain on the forefront of science in all that we do. We currently have Centers of Excellence in outcomes research, health economics, epidemiology and statistics and a Center of Excellence in pricing and reimbursement is under development.

The goals of these centers are to:

- Guarantee Evidera remains the scientific leader in each discipline
- Ensure the application of best practices in these core disciplines
- Develop novel methodologies for incorporation into Evidera offerings
- Enhance our flexible and integrated response to client priorities through further scientific collaboration across the company
- Promote best-in-class capabilities, skills and training in these core disciplines

EVIDERA WELCOMES NEW SENIOR STAFF

JEFF ANDERSON, PHD
Principal Consultant, Strategic Solutions

Jeff Anderson is responsible for leading value demonstration strategy (VDS) projects and supporting other scientific efforts to ensure the broader Evidera offer is both coherent and integrated across our scientific staff and across programs of work. In this role, Jeff has client engagement and business development responsibilities throughout the European market and is based out of the London, UK, office.

Jeff has led strategic programs and projects covering the broad range of HTA and HEOR disciplines in the biopharmaceutical and medical devices industries, working in a variety of disease areas, including respiratory, cancers, urology and ophthalmology. Additionally, he has been involved in supporting industry submissions to NICE and has a deep understanding of the NHS payer/provider landscape.

Previously, Jeff was director of the consulting group at the School of Health and Related Research (ScHARR) at the University of Sheffield. He also led a core value demonstration module on ScHARR's master's program for International Health Technology Assessment, Pricing and Reimbursement. Before that, he held various consulting positions and has been a senior commissioner for the NHS in the UK health system. He received his PhD in medical sciences from the University of Exeter.

ALI "AL" ARTAMAN, MD, MHA, MS, PHD

Research Scientist, Retrospective Observational Studies

Al Artaman has extensive experience in clinical, public and global health epidemiology. In his current role, he acts as principal investigator or co-investigator on descriptive and observational epidemiological studies in the U.S. and Europe. Prior to joining Evidera, he worked as an epidemiology manager in southwest and eastern Ontario, Canada, dealing with disease surveillance and complex survey and trend analyses. He was also a coordination committee cochair of the Canadian Alliance for Regional Risk Factor Surveillance, and he is currently an expert for the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD 2013) coordinated through the University of Washington.

In the mid-2000s, while pursuing graduate studies in epidemiology at Michigan State University, Al coordinated a CDC-funded data center for national autism surveillance and research. Subsequently, he authored research grant proposals and managed and completed an NIH-funded retrospective safety study of perinatal interventions and childhood leukemia in Michigan. He has consulted for a number of medical and research centers around the world dealing with system-level planning related to health information and data management, and he began his career as a general practitioner in west Asia.

XAVIER BADIA, MD, MPH, PHD

Sr. Research Leader, Europe
Sr. Leader of European Market Development

Xavier Badia holds a senior level position at Evidera, providing high-level strategic and scientific leadership in health economics, outcomes research and market access. In his role, he offers clients in-depth expertise in European market access and evidence generation, in addition to facilitating communication between Evidera and European decision-making bodies. Xavier has extensive experience in clinical research, working in the public sector and as a consultant for numerous major projects. He specializes in evaluating and developing innovative pricing agreements, health policy, clinical effectiveness and patient-reported outcomes.

In his career, Xavier has led projects in a multitude of therapeutic areas, including oncology, endocrinology, cardiovascular, osteoporosis, CNS and rare diseases, among others; has published more than 180 papers in peer-reviewed journals, six books and several book chapters; and also serves on several editorial boards. He is an active member of the International Society for Pharmacoeconomics (ISPOR), the EuroQol Group, Centre for Biomedical Network Research on Rare Diseases (CIBERER) and the Spanish Rare Disease Registries Research Network.

Company News

EVIDERA WELCOMES NEW SENIOR STAFF (CONT.)

BELA BAPAT, MA
Research Scientist, Retrospective Observational Studies

Bela Bapat has worked in the field of health economics and outcomes research for more than 11 years. She has extensive experience in healthcare claims database analysis, cross-sectional and longitudinal survey analysis and analysis of data from retrospective chart abstractions. Bela has worked in various therapeutic areas, such as attention deficit hyperactivity disorder, meningococcal disease, abdominal adhesiolysis, Dupuytren's contracture, adhesive capsulitis, Peyronie's disease, chronic hepatitis C, chronic kidney disease, contrast-induced nephropathy, myelodysplastic syndrome and a multitude of oncology indications. She has coauthored research published in multiple peer-reviewed journals, and her research has also been accepted for presentation at numerous professional conferences and workshops.

XIAOYUN (LUCY) PAN, PHD
Research Scientist, Retrospective Observational Studies

Xiaoyun (Lucy) Pan has more than 10 years of academic experience in health economics and outcomes research (HEOR), as well as industry HEOR experience at two pharmaceutical companies. Lucy's expertise includes claims data analysis, such as SEER-Medicare claims database, IHCIS and premier database, as well as statistical modeling expertise in multivariate regression, Cox-proportional hazard regression, Kaplan-Meier estimators and instrumental variable estimation.

Prior to joining Evidera, she was an assistant professor in health outcomes research at the Department of Pharmaceutical System and Policy, School of Pharmacy, West Virginia University. Lucy has experience researching in a variety of therapeutic areas, including oncology, multi-comorbidity, diabetes, Crohn's disease, arthritis and chronic obstructive pulmonary disease. As a principal investigator or co-investigator, Lucy has won scientific grants for projects that were insightful and actionable in addressing health outcomes and policy issues. She has had multiple articles published in peer-reviewed journals and abstracts published at national and international conferences. She received her doctorate and master's degree in pharmaceutical socioeconomics from the University of Iowa.

SENIOR LEVEL PROMOTIONS ANNOUNCED

ANURAAG KANSAL, PHD
Director, Disease Simulations
Anuraag is also a senior research scientist and is based in Bethesda, MD.

SONJA SORENSEN, MPH
Sr. Director, Modeling and Simulation
Sonja is also a senior research scientist and is based in Bethesda, MD.

ALEX WARD, PHD, MRPHARMS
Director, Operations and Process
Alex is also a senior research scientist and is based in Lexington, MA.

IPEK OZER STILLMAN, MSC
Sr. Director, Modeling and Simulation
Ipek is also a senior research scientist and is based in Lexington, MA.

EVIDERA'S BETHESDA HEADQUARTERS' SUITE NUMBER HAS CHANGED

Evidera's corporate office in Bethesda, Maryland, has moved to a new floor. While we remain in the same building, with the same phone numbers, our suite number has changed from Suite 600 to Suite 1400. Please make a note of our new address for future correspondence.

EVIDERA
7101 WISCONSIN AVE., SUITE 1400
BETHESDA, MD 20814

SAVE THE DATE
MAY 15, 2015

PATIENT-REPORTED OUTCOMES MEASUREMENT INFORMATION SYSTEM (PROMIS®)

From Basics to Applications in Clinical Research, Practice, and Population Health

PHILADELPHIA MARRIOTT DOWNTOWN • PHILADELPHIA, PA, USA

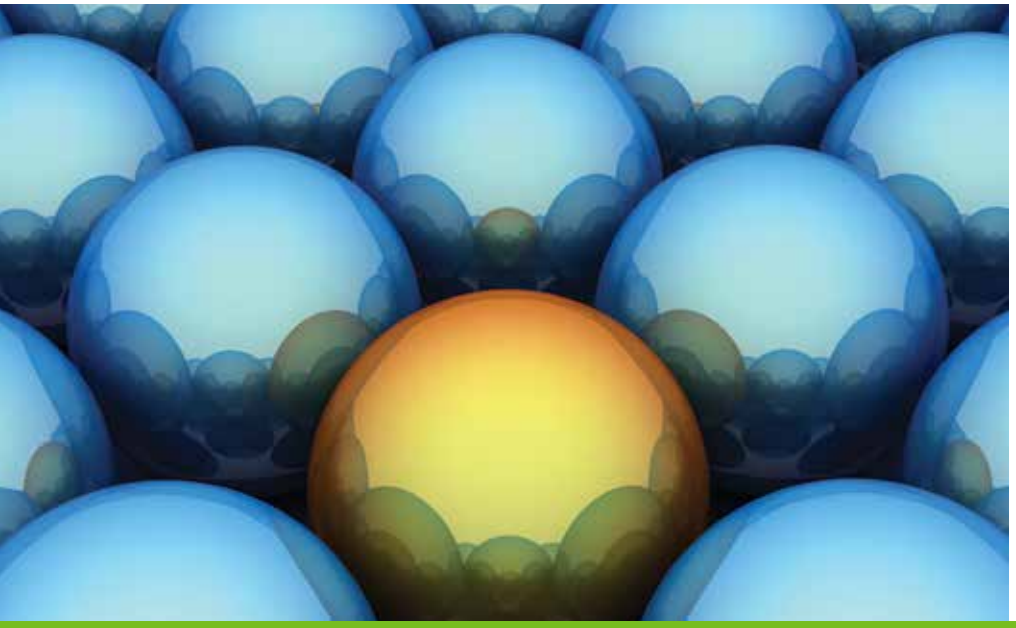
PURPOSE

The PROMIS Health Organization, on behalf of the Patient-Reported Outcomes Measurement Information System (PROMIS) network, will host an all-day interdisciplinary forum to examine conceptual, methodological, clinical, and research aspects of assessing and using patient-reported outcomes (PROs). This scientific meeting will bring together academic researchers, government scientists, clinicians, clinical researchers, industry representatives, and experts in outcomes measurement to discuss applications of PROMIS in health care and outcomes research and practice and the state of the science in this critical field. It will feature keynote and plenary presentations from leaders in the field, numerous papers in concurrent breakout sessions, posters, and ample time for discussion among all participants.

Information about registration and abstract submission for oral and poster presentations will be forthcoming.

The Planning Committee for this conference includes Dennis A. Revicki, PhD, Senior Research Leader and Senior Vice President, Outcomes Research, Evidera.

If you have questions, please contact:
Julie Kay, MPH
312-503-1725
Julie-kay@northwestern.edu



Evidera's Complimentary **Webinars**

Tuesday, November 18, 2014
10:00 AM EST

Market Access for Orphan Drugs in China

PRESENTERS

Susanne Michel, MD, European Practice Lead, Payer Strategy, Evidera

Xia Chen, PhD, Consultant, Payer Strategy, Evidera

RECENT WEBINARS AVAILABLE ON DEMAND

New High-Priced Treatments for Hepatitis C Infection: Have US Payers Reached a Tipping Point?

PRESENTERS

Cheryl Ball, BSFS, U.S. Practice Lead, Global Payer Strategy, Evidera

Sandra Ford, BSc, Managing Consultant, Global Payer Strategy, Evidera

Technology Innovations in the Development and Collection of Patient-Reported Outcomes (PROs)

PRESENTERS

Karin Coyne, PhD, MPH, Senior Research Leader and Scientific Director, Outcomes Research, Evidera

Andrew Cox, PhD, Research Scientist, Retrospective Observational Studies, Evidera

Sonya Eremenco, MA, Director, ePRO New Products, Outcomes Research, Evidera

Hilary Wilson, PhD, Research Scientist, Outcomes Research, Evidera

Methods for Patient-centered Endpoint Selection in Rare Disease Drug Development Programs

PRESENTERS

Kathy Wyrwich, PhD, Senior Research Leader and Executive Director, Center of Excellence - Outcomes Research, Evidera

Margaret Vernon, PhD, Senior Research Scientist and European Director, Outcomes Research, Evidera

For more information on any of Evidera's upcoming or on demand webinars, visit www.evidera.com/webinars.

Incredible People Do Incredible Work at Evidera

We develop and retain the industry's most talented scientists and life sciences professionals to enrich professional careers and personal lives.

EVIDERA: WHERE YOUR WORK HAS MEANING

We're committed to helping science and the people who do it. We prepare our teams to work side-by-side with industry experts and a broad array of client stakeholders and healthcare professionals.

MEANINGFUL WORK AT EVERY LEVEL

We assess candidates across a variety of scientific and operational functions. From leaders in their fields, to those who are new to the industry, we employ people who have a proactive mind-set when it comes to the work they do and helping the people they work with.

Evidera is always looking for innovative researchers with experience in our key research areas.

- Epidemiology
- Health Economics
- Meta Research
- Modeling and Simulation
- Outcomes Research
- Payer Communications
- Payer Strategy
- Retrospective Observational Studies
- Statistics

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

Join Our Team. Make Your Work Matter.
careers.evidera.com

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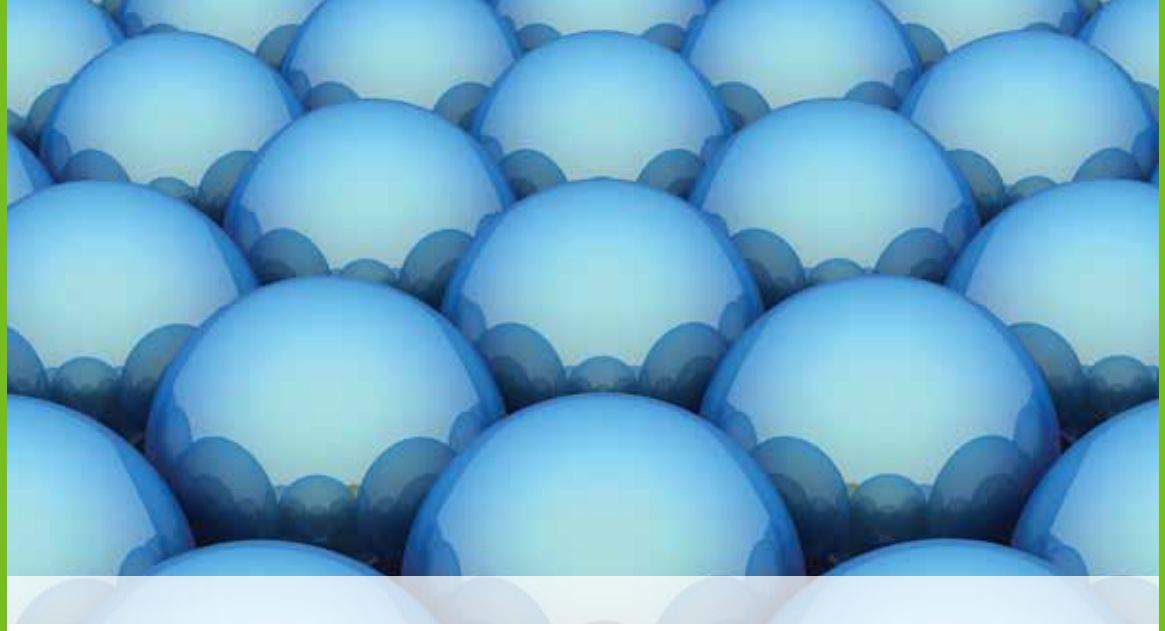

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The Evidence Forum is an official publication of Evidera, providing evidence, value and insight through evidence-based solutions that enhance patient care and help people live longer, healthier lives.

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