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MAY 2015

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Advancing Patient-Centered Outcomes Research:

An Interview with Dr. Bryan Luce and Dr. Lori Frank of PCORI





Dr. Bryan Luce

Dr. Lori Frank

Healthcare decision making can be a minefield to navigate. With treatment options increasing, reimbursement issues constantly changing, and an abundance of information that can be difficult to digest and comprehend, patients, caregivers, families, and clinicians are often faced with complex and challenging healthcare decisions. They need accessible, trustworthy information in order to make the right decisions, and this information is often not available or difficult to understand and use effectively.

The Patient-Centered Outcomes Research Institute (PCORI) was established as part of the U.S. Patient Protection and Affordable Care Act of 2010 to help address some of these challenges by closing the gaps in evidence needed to improve key health outcomes. To this end, its efforts include identifying critical research questions, funding patient-centered comparative clinical effectiveness research (CER), and disseminating the results of this research in ways that end users will find useful and valuable.

To better understand the goals and activities of PCORI, members of Evidera's Centers of Excellence in Health Economics, Outcomes Research, Epidemiology and Statistics put their questions forward, and we posed them to Bryan Luce, PhD, MS, MBA, Chief Science Officer, and Lori Frank, PhD, Program Director, Science, Research Integration and Evaluation, both of PCORI. Dr. Luce previously founded the outcomes research firm MEDTAP® International, serving as its chairman, president, and chief executive officer, and was the senior vice president for science and policy at United BioSource Corporation. Earlier, he was director of Battelle's Centers for Public Health Research and Evaluation; director of the Office of Research and Demonstrations, Centers for Medicare and Medicaid Services; and a senior analyst at the Office of Technology Assessment of the U.S. Congress.

Dr. Frank previously worked as a director in health outcomes and pharmacoeconomics at MedImmune, LLC, and before that, she spent 13 years with MEDTAP International and United BioSource Corporation where she was a senior research leader and executive director of the Center for Health Outcomes Research. She also initiated and served as principal investigator of the Cognition Initiative, a multi-sponsor, patient-reported outcomes (PRO) development consortium and continues in an advisory role for that work, now part of the Critical Path Institute PRO Consortium.

We've been hearing a lot about patientcentered outcomes research (PCOR) and there seem to be differing opinions on its definition. How do you describe PCOR?

Dr. Frank: PCOR is research that considers patients' needs and preferences while focusing on outcomes that are most important to them. It investigates what works, for whom, and under what circumstances to help patients and other stakeholders make informed decisions about health and healthcare options. The essence of the PCORI definition of patient-centered outcomes research is the evaluation of questions and outcomes meaningful and important to patients and caregivers. This definition rests on the axiom that patients have unique perspectives that can change and improve the pursuit of clinical questions. An important point to mention is that the PCORI Board of Governors went through a participatory process when they were coming out with this definition, including soliciting public comment, which is fairly unusual to see from a funding agency but also shows that they really took the public input to heart in all areas when developing PCORI.

Are you seeing people using the term in different ways or are you seeing any alignment in the definition?

Dr. Frank: We are seeing some variation in how the notion of patient-centered outcomes research is being expressed, but over the last three years I've seen some narrowing of the definition and increasing consensus.

Dr. Luce: My impression is there is less confusion about the definition of PCOR as opposed to how the concept is applied to research and research topics. So from a PCORI standpoint, we reinforce our definition by explaining that PCORI is a funder and we have certain funding requirements that interact with that definition, including ensuring that the comparative effectiveness research that we fund is patient-centered.

"...there is definite interest (from industry), but I think they can be more active. Payers are absolutely interested. We have reached out to them and we have seen some outreach from payers to us."

– Dr. Luce

Can you provide a bit more detail around the use of comparative effectiveness in PCORI's mandates and funding?

Dr. Frank: PCORI is charged with funding comparative clinical effectiveness research. We have five main research priority areas:

- Assessment of Prevention, Diagnosis, and Treatment Options
- Improving Healthcare Systems
- Communication and Dissemination Research
- Addressing Disparities
- Accelerating Patient-Centered Outcomes Research and Methodological Research

Four of these areas have as a requirement for funding that the applications involve a comparison that meets our definition of comparative effectiveness research. The fifth area is focused on methods where we fund basic methods research and focus on improving methods for comparative effectiveness research, and infrastructure, which focuses on PCORnet, the National Patient-Centered Clinical Research Network that we are developing with 29 health data networks.

How do you see the biopharma industry engaging in patient-centered outcomes research, and what opportunities do you see for PCORI and the pharmaceutical/biotech/ medical device industry to work together?

Dr. Frank: There are many definitions of end users or stakeholders of the research we are funding, and industry is a really important one. Not surprisingly, Bryan has been leading the way to make sure that PCORI's ability to work with all stakeholders is well known, especially within industry.

Dr. Luce: We actually had a very focused workshop on March 30 with representatives of the pharmaceutical and biologics industries, and we held another on March 31 with the medical device industry to discuss PCORnet. These meetings included talking to and, more importantly, listening to industry about their interest and needs in working in an infrastructure like we have in PCORnet, and part of that is in patient engagement and patient-centered research.

Dr. Frank: I would also add that there are members of industry on our advisory panels, including the patient engagement and clinical trial advisory panels, and representatives from industry also participate in evaluating

funding applications for PCORI as stakeholder reviewers. PCORI has board and methodology committee members from industry. So industry is more than welcome, and actually recruited, to participate in PCORI activities.

Have you seen a lot of interest from industry?

Dr. Luce: Yes, there is definite interest, but I think they can be more active. Certain companies are highly committed, but in a broad sense. I don't think industry has engaged as much as we would like and I think it would be in the best interest of industry to engage more.

How do you see the work at PCORI improving health outcomes for Americans in general?

Dr. Frank: It is the goal of everything that we're doing at PCORI — to improve health outcomes ultimately. The research that we fund has as a requirement that it have an impact on the health of the population. So, before research is even selected for funding, we ask everyone to evaluate whether it can ultimately improve health outcomes.

Dr. Luce: The other component of that is that we have a strong belief that by the very act of engaging real-world decision makers — those who would ultimately be the consumer of the evidence — in our entire process, the evidence for decision making has a much higher chance of being adopted and used, and potentially changing the practice of how evidence is gathered and considered.

"...the inclusion of patients and caregivers highly enriches the discussion and process, so that we end up funding research that meets high standards for technical merit but is also meaningful to patients."

– Dr. Frank

The research applications that we review for potential funding are actually prioritized by multi-stakeholder merit review panels that include patients, researchers, and other stakeholders. These panels of 20-25 individuals come together, debate and score the merits of individual studies, and final decisions are made based on those scores. So again, this is a unique system where patients and researchers are all at the table together and are all considered equal members of the team.

Our merit review criteria include not only the impact of the condition on the health of individuals and populations, the potential to improve healthcare and outcomes, and technical merit, but also unique criteria that includes patient-centeredness and patient stakeholder engagement. It is our belief that by requiring all of these elements, not only will the research itself improve, but the speed of its uptake and ultimate impact on health outcomes will also increase.

When participating in merit review, do patients evaluate the applications only in areas that they are personally affected by or do they cross therapeutic areas and indications?

Dr. Frank: Great question, and it's one we've really spent a lot of time talking about. We encourage all of the reviewers, including the patient reviewers, to let us have the benefit of their general perspective, and if there's a specific therapeutic area in which they have expertise, that will definitely be considered.

It's challenging to make sure we're getting the right voices heard, and we have put a lot of thought into this process. We have a pretty robust and, we think, effective training program that educates patients and other non-scientific reviewers on how to evaluate research proposals. We also acknowledge that the non-scientists might not feel comfortable sitting at a table with scientists who are used to writing and reviewing these funding applications. So, PCORI provides mentors who have been through the process and can speak to them from experience and guide them so they are able to provide the best review possible.

We also focus on bi-directional training and communication, including training the scientific reviewers on how to interact with the non-scientists, to reduce concern about intimidation or respect when they're debating the scientific merits of a proposal. We also reinforce that patients often have something they can teach the research community and that all parties should engage in educating and listening to the others on the team. It definitely takes extra time and the entire process took some honing, but it has turned out to be quite impressive and it really works. Overall, we have found the inclusion of patients and caregivers highly enriches the discussion and process, so that we end up funding research that meets high standards for technical merit but is also meaningful to patients.

How do you go about identifying patients to participate in PCORI activities?

Dr. Frank: We have a whole patient engagement team, a group that focuses on engagement with the patient community, and this includes individual patients as well

as patient advocacy organizations. For participation in activities like our panels and merit review teams, there is an application process. So, we have a PCORI list of those who have applied, but we are always doing outreach beyond that to encourage new participation. Our engagement team has engagement awards and funding available to help support infrastructure to help connect patients with researchers, for example.

In regard to your funded projects, do you have results from projects yet? And what happens to those results? How will they be used?

Dr. Frank: Well, PCORI is not just interested in getting good research funded, but also in making the results available as quickly as possible. Our first round of funding for our pilot projects was announced in May of 2012. There were 50 pilot projects. Those were two-year projects, shorter than normal, and they are either final or just finishing up. There has already been some dissemination in peer-reviewed literature and also in grey literature, forums other than peer-reviewed literature that help get the word out to stakeholders who need to know the information.

PCORI is like any other funder in that the results of the research belong to the awardees. However, our legislation requires that at least the basic results and data from our funded research are made available within 90 days of our receipt of the final report about a project. We also require the research be registered with the public site appropriate to the study design, such as ClinicalTrials. gov, and we will post research reports on our website.

Do you get the sense that payers in the U.S. are reaching out for PCOR information?

Dr. Luce: Payers are absolutely interested. We have reached out to them and we have seen some outreach from payers to us. However, we would like to see them more engaged. The interest and participation seem to be more focused on some of our big trials that have funding in the \$10 million range. For these large trials we require that applicants have a robust study team that includes major organizations, national organizations, and key stakeholders — including payers, clinical specialty societies, patient advocacy groups, etc. As a result, many of the research applications that we are funding will include payer input since one of the considerations in our funding decisions is whether the right stakeholders are part of the research, and that includes payers.

PCORI is, obviously, U.S. focused as its creation was part of the U.S. Affordable Care Act. Is there any non-U.S. involvement or do you see PCORI activity influencing treatment decisions outside of the U.S.?

Dr. Frank: PCORI's intent and mandate is to help U.S. citizens, and although anyone can apply for PCORI funding, the research must improve the health of people residing in the U.S. To date, almost 100 percent of our funding has been awarded to U.S. investigators.

We are always looking for ways in which the PCORI model is influencing others, and we certainly have been in conversations with different groups who also have public involvement in research around the world. We are interested in how those groups include public involvement, so we have a formal outreach program to make sure that we're not missing out on what's being learned elsewhere. But increasingly, we hear that those groups are watching us and they want to see how we are handling the process, surveying people, what questions we are asking about engagement, etc.

Dr. Luce: One particular area is rare diseases. This is one area that may require reaching beyond U.S. borders in order to have enough patients to do research. We have a rare disease advisory panel and they are currently discussing this, so we could see more involvement outside the U.S. in research for those specific cases. But again, the final research would need to benefit U.S. citizens.

Are there any counterparts to PCORI in other countries that you're aware of, or is PCORI really unique in its focus on patient-centered outcomes research?

Dr. Luce: I would say PCORI is unique, especially because of the emphasis on comparative effectiveness research and our requirement for engagement of end-users in the research.

We have seen a fair amount of interest from other countries that have sent delegations to meet with us, including Canada, the United Kingdom, and Australia, and in a number of cases, there is some sort of government funded, patient-centered endeavor for research. It is not clear if the PCORI model of patient and stakeholder engagement has been fully adopted any place else, but there is a clear interest in the whole process, including countries outside of the U.S.

Is there anything else important to note about PCORI that you think our readers would be interested in?

Dr. Frank: I just want to re-emphasize the very important point that we engage stakeholders in everything we do, so it's a requirement for the research we fund. They help us identify the topics we pursue for funding, evaluate the research itself, and get the word out about the research once it is finished.

Dr. Luce: One area I wanted to expand on is the national priorities that the board has set for trial applications. That includes what the field calls clinical comparative effectiveness research, which includes a drug-drug, drug-device, drug-procedure, and drug-usual care studies — clinical trials or observational studies for that matter. Another priority is improving healthcare systems, where we look for comparative ways to organize the care or systems-level intervention, such as transitional care. For example, we have a big project on alternative ways to prevent serious falls in the frail and elderly, which is a whole systems issue and not an individual clinical intervention. Another national priority is studies addressing disparities, recognizing that vulnerable populations have all types of problems relative to health, and that there are alternative ways to address them. An example here might be an asthma program that may be highly effective when it comes to trials and in major populations, but it may not be effective in a Hispanic or an inner-city population, or a frail and elderly population. We also have specific research programs focused on alternative ways to communicate and disseminate useful research.

PCORI has gotten a lot of praise in the news and it is obvious there is a lot happening. Is there something for each of you that you're particularly excited about or something that we have to look forward to?

Dr. Luce: The big thing you have to look forward to is the outcome of several hundred million dollars' worth of comparative effectiveness research. If we are doing the job we were created to do, and I think we are, there will be a great deal of research evidence across many, many different areas of healthcare clinical interests that will be highly focused on the real concerns of all key stakeholders. That includes patients, doctors, payers, clinical guideline committees, etc. The questions that those groups have that no one has been funding will start to be answered. Initial results are starting to come out, but within the next year we should start to see an increase in real research outcomes. And, we're attempting to link different studies with different teams, even bringing together different groups that are working in the same general area, which should really make a difference. If we are doing our job right, you will see truly useful evidence for decision making.

Dr. Frank: I just want to endorse that answer. PCORI is funding research for important questions that need to be answered, and PCORI has a specific interest in making sure that the results of that research are heard by the people who need it.

"...PCORI has a specific interest in making sure that the results of that research are heard by the people who need it."

– Dr. Frank

Dr. Luce, I understand that you are retiring this fall. What are your goals during your remaining time with PCORI, and what are your future plans?

Dr. Luce: Yes, I announced last year that I would be retiring from PCORI in September 2015. The main goal of my office, and certainly myself, is to fund truly impactful comparative effectiveness research that will make a difference in improving healthcare. And as far as my future after PCORI, who knows what I'll be doing, but I'll probably not totally disappear.

As we conclude, Dr. Frank, do you have specific goals that you want to accomplish at PCORI?

Dr. Frank: My role at PCORI focuses on leading the evaluation of PCORI processes and process improvement in general, with the merit review process being an important part of that. I want to be sure that we're always collecting the right information so that at any time we can know for ourselves and share with others how well PCORI is doing against its mission and against its stated goals.

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2015

2015

0%

10% 20% 30% 40%

ACADEMIA

(86%)

BUT ITS IMPACT ON DECISION-MAKING IS STILL 3-5 YEARS DOWN THE ROAD.





50%

KEY GROUPS IN CONDUCTING CER

INDUSTRY NIH (48

70%

80%

60%

(60%)

90%

100%

KEY PLAYERS IN DISSEMINATING CER



For key roles, stakeholders were asked to choose among the Agency for Healthcare Research and Quality (AHRQ), the National Institutes of Health (NIH), the Food and Drug Administration (FDA), the Patient-Centered Outcomes Research Institute (PCORI), academia, private health plans and the biopharmaceutical industry. N=122 for Stakeholders Surveyed. N=115 for Importance of CER. N=114 for Impact of CER in the Past Year and 1 Year; N=115 for the Next 3 Years and Next 5 Years. N=117 for remaining figures



View the complete survey results and related materials and download our booklet, 2015 Comparative Effectiveness Research and the Environment for Health Care Decision-Making at www.npcnow.org/cersurvey15.

Will the Growing Reliance on Real-World Data Fuel Fundamental Changes in the Way We Approach Database Analyses?

Stephanie Reisinger Vice President, Technology Solutions Gary Schneider, MSPH, ScD Epidemiologist Matthew Reynolds, PhD Vice President, Scientific Development

Electronic medical records and administrative claims databases, which contain "real-world" patient data collected at the point of care, have been used in pharmacoepidemiologic research for many decades. One of the first published database studies appeared in 1979, evaluating the association between the use of hormone replacement therapy in menopausal women and endometrial cancer using a database from the Group Health Cooperative (GHC) of Puget Sound.¹ Since that time, the focus of non-interventional research using real-world patient data has been relatively narrow, used mainly to fill information gaps not addressed through controlled clinical studies. However, the industry is currently in the middle of a fundamental shift in both the availability of, and reliance upon, real-world databases for evidence generation.

Several trends have converged to catalyze this shift including:

- 1. The demand for product value demonstration by an increasingly diverse group of stakeholders, including regulators and payers
- 2. Rapid proliferation, both in number and size, of available real-world data sources
- 3. Technological advances supporting the storage and management of "big data" assets

- 4. The development of specialized analytic methodologies to control for the types of bias found in real-world data sources²
- 5. A growing ability to support hybrid study designs, where patients analyzed retrospectively can be re-identified for prospective research

No longer just a sideline, the evidence generated from realworld data is rapidly becoming an integral component of new product evidence strategies.³ At the same time, the growing volumes and heterogeneity of real-world data sources are creating analytic environments that are disorganized, inefficient and increasingly difficult to manage. Traditional database analytic approaches may be inadequate to fully take advantage of the evidence generation potential offered by this new era of real-world data.

Issues with traditional database analysis approaches in today's environment

Although most real-world databases contain similar information about patients collected at the point of care, these databases can vary significantly in both the structure and syntax of the data as well as the nomenclature used to represent pharmaceutical products and patient healthcare conditions. Because of these differences, the traditional analysis approach requires the development of a custom program written to answer a specific question against a specific database. This relies heavily on the availability of programmers with a sufficient understanding of the underlying database, a rate-limiting and inefficient approach that usually requires a single database to be selected for each study. This "one database per study" approach to evidence generation does not lend itself well to the growing demand for real-world evidence. Issues with the current approach include:

- **Not efficient:** Evidence generation is constrained by available programming resources and the knowledge of the programmers, and requires custom programming for each analysis.
- **Not transparent:** Patient and clinical event selection assumptions and algorithms are tied to the specific format of the database and embedded within the program code.
- **Not reproducible:** Format and programming differences among databases make it inefficient to execute and difficult to meaningfully compare evidence generated across disparate data sources.

Fueled by an increasing reliance on real-world evidence, pharmaceutical decision makers are demanding broader, more efficient evidence generation capabilities across heterogeneous real-world data sources, and new approaches are urgently needed to address this growing demand.

Standardization can help to address key issues

The issues described above are well known by most database researchers, and over the past seven years several organizations have focused on understanding and addressing them. In the United States, the Food and Drug Administration's (FDA) Sentinel Initiative,⁴ the Observational Medical Outcomes Partnership (OMOP),⁵ and the Observational Health Data Sciences and Informatics (OHDSI) collaborative,⁶ and in Europe the EU-ADR project,⁷ among others, all focus on the efficient use of real-world databases for evidence generation. A common theme across all these organizations is standardization, which falls into two broad categories: standardization of data and standardization of analytics.

Fueled by an increasing reliance on realworld evidence, pharmaceutical decision makers are demanding broader, more efficient evidence generation capabilities across heterogeneous real-world data sources, and new approaches are urgently needed to address this growing demand.

- **Data standardization using a common data model:** There have been several articles written about the development and use of a common data model (CDM) for analysis of real-world databases.^{8,9} Although a CDM can be complex to implement, its basic purpose is fairly straightforward — to create a standard data format (structure and syntax) accommodating the critical data elements required to support the desired evidence generation capabilities efficiently. Some CDM designs, such as the OMOP CDM, also include a standardized vocabulary for drugs and conditions.¹⁰
- Analysis standardization using modular programs: A primary benefit of implementing a CDM is that standardized analytic routines can be written for the CDM and executed against any real-world database that has been transformed into the CDM format. Furthermore, key patient selection and analysis variables within each standardized module can be parameterized and entered by the user at analysis time. These "modular programs" can be executed by non-programmer researchers since they do not require any custom programming. Both the FDA's Sentinel Initiative and the OHDSI collaborative have included the development of parameter-driven modular programs as part of their respective research.^{11,12}

A standardized analysis example

Below is a simplified illustration of a standardized analysis. Figure 1 provides a partial logical representation of a patient record in the OMOP CDM format, including demographic and clinical data. All the patient and clinical variables used in the example below are commonly available in real-world databases.

Figure 1: Partial patient record in OMOP CDM format

Patient	Data		
Gender	Female		
Age	62		

Clinical Data	т	Timeline		
Enrollment	1/1/2010	12/30/2011		
Atrial fibrillation	* 8/ <u>12/2</u> 010			
Coumadin*	8/13/2010	0 10/28/2011		
Cerebrovascular	accident*	5/1 <mark>9/2</mark> 011		
*standard vocabulary				

Table 1 and Figure 2 illustrate the steps and associated parameters required to perform a standardized analysis to answer a common type of analysis question.

Table 1: Example of modular program steps andassociated user parameters

Analysis question:

How many female patients over age 60 who have been diagnosed with atrial fibrillation were also treated with Coumadin within 7 days of their diagnosis? Of those patients, what percentage had a stroke in the 365 days following diagnosis?

Мо	dular Program Steps	User Parameters
Step 1	Select all patients with user specified characteristics	Female; > Age 60
Step 2	Restrict the patients selected above to only those patients with user specified condition	Atrial fibrillation
Step 3	Further restrict the selection to those patients who were treated with user specified drug within user specified time frame	Coumadin; within 7 days after atrial fibrillation diagnosis
Step 4	Of those patients, what percentage were diagnosed with user specified condition within user specified time frame	Cerebrovascular accident; within 365 days after atrial fibrillation diagnosis

Figure 2: Standardized analysis applied to a patient record in the CDM format

Patient		
Gender	Female	Step 1
Age	62	

Clinical Data	Timeline
Enrollment 1/1/20	010 12/30/2011
Atrial fibrillation* Step 2	2 8/12/2010 < 7 days
Coumadin* Step 3	8/13/2010 10/28/2011
Cerebrovascular accider	<pre>< 365 days nt* Step 4 5/19/2011</pre>
*standard vocabulary	

Figure 2 provides a brief illustration of a standardized analysis, showing the analysis steps and how they are applied to the CDM. Although not appropriate for all analyses, there are many types of analyses that lend themselves well to this type of parameter-driven approach, including exploratory and descriptive analyses, analyses that are performed repeatedly (e.g., ongoing monitoring), common analytic calculations such as rates of diseases or outcomes, and characteristics of product exposure, to name a few.

"Collaborative analytics": A new era of real-world evidence generation

The potential for standardization to significantly improve the efficiency of real-world database analytics has been demonstrated through recent studies¹³ as well as by research presented in this issue of *The Evidence Forum* in the article: *Collaborative Analytics in Action: A Case Study Focused on Treatment Patterns.* Yet there is another more subtle and potentially very powerful benefit of standardization that could fundamentally change the current database analytics paradigm.

Coding algorithms, which are defined as some combination of diagnosis, procedure, drug; or lab value codes and/or condition that reliably identify a specified health event from real-world databases, have recently received attention. Both the FDA Sentinel Initiative and the OMOP have published coding algorithms for various health outcomes of interest (HOIs) that are of particular interest to drug safety researchers.^{14,15} Figure 3 shows an example coding algorithm for aplastic anemia. In an ideal world, all key clinical variables in a database study would be defined via coding algorithms, but in practice most of the algorithms required to identify clinical variables are custom developed (and redeveloped) for each study and database.¹⁶

Figure 3: Example coding algorithm for aplastic anemia from the OMOP HOI library

Example coding algorithm for Aplastic Anemia

ICD-9:284.0*, 284.8*, 284.9 AND within 60 days prior to the diagnostic code Diagnostic procedure code for bone marrow aspiration or biopsy

In a standardized analytic environment such as the one described above, user parameters can be developed to standardize the implementation of coding algorithms for important clinical events. These parameters can be curated and stored in a clinical event library and later searched, shared, and re-used in analyses across an entire organization. Simply selecting the clinical event of interest from the library copies the appropriate parameters for that clinical event/coding algorithm into the desired analysis module. The current analytic environment is based mainly on custom, one-off analysis programs developed in isolation against a single database for each study. Standardization enables an innovative environment of "collaborative analytics" where modular programs and clinical event definitions can be collaboratively developed, shared, and re-used within and across organizations and, thinking even bigger, across the entire industry. In addition, because modular programs and clinical event definitions can be executed against any data-source in CDM format, analyses can be efficiently reproduced across disparate databases and organizations, and the results of these analyses can be meaningfully compared.

Considerations and limitations

Although standardized analytics offers great potential to improve the power and efficiency of real-world evidence generation, there are some limitations to this approach.

- **Time and resource commitments:** The implementation of a CDM and a standardized analytic environment is complex and requires a commitment of time and resources.
- Information loss: The process of mapping the raw source data into the CDM may result in some data loss, particularly if non-standard drug and condition codes are found within the source data. To mitigate this issue, some CDMs, such as OMOP, allow the native codes to be stored and used for analysis in addition to the standardized vocabulary.
- Clinical and data content expertise: Standardization does not reduce the need to have clinical, epidemiological, and data content experts involved in the development of study protocols and analysis parameters and for interpretation of results.
- Interoperability: Not all types of analysis are well suited for standardization. Organizations will continue to have the need for custom analysis programs to be written for detailed and difficult analytic tasks. Interoperability between the standardized and traditional analytic environments is necessary for researchers to move back and forth between environments.

• **Quality of Output:** Standardized analytics are powerful and efficient, creating an environment with a potential for misuse by untrained and inexpert users. Formal user training requirements, access limitations, and peer review processes should be developed and implemented to ensure analysis results are of the highest quality.

To reach the full potential that standardization can provide, the industry should consider moving toward the adoption of an industrywide common data model standard for real-world analytics.

Where do we go from here?

Standardized analytics offers great potential to address growing demands for efficient real-world evidence generation, but we are only at the beginning of our understanding of how to best integrate this approach into existing evidence generation schemes. To reach the full potential that standardization can provide, the industry should consider moving toward the adoption of an industrywide common data model standard for real-world analytics. Given that there are multiple organizations promoting different CDM versions, this statement may seem controversial. However, existing CDM standards proposed by different organizations are more similar then they are different, and recent research has provided insight into the pros and cons of each model.¹⁷ An ideal standard would incorporate the best features of each.

Moving forward, collaborative research organizations such as OHDSI are critical in providing a platform to advance the science of standardized analytics while integrating the input of diverse stakeholders. Finally, commercial technology and data providers should incorporate non-proprietary, open standards into their offerings where commercially feasible, ensuring greater interoperability and integration across all commercial real-world data offerings.

For more information, please contact <u>Stephanie.Reisinger@evidera.com</u>, <u>Gary.Schneider@evidera.com</u> or <u>Matthew.Reynolds@evidera.com</u>.

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Collaborative Analytics in Action: A Case Study Focused on Treatment Patterns

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Introduction

For the past seven years, Evidera scientists have been on the forefront of research into the use of a Common Data Model (CDM) to enable standardized healthcare analytics, participating as the principal investigator on several Observational Medical Outcomes Partnership (OMOP) research initiatives^{1,2} as well as a collaborator with the Observational Health Data Sciences and Informatics (OHDSI) program.³ A companion article in this issue of The Evidence Forum, "Will the Growing Reliance on Real-world Data Fuel Fundamental Changes in the Way We Approach Database Analyses?" describes in detail how a standardized approach to database analysis can enable an environment of "collaborative analytics" where analysis programs and clinical event definitions are collaboratively developed, shared, and re-used within and across organizations. This article describes the results of a collaborative analytics research project performed by Evidera scientists in collaboration with scientists at GSK and BMS. The research has been presented at ISPOR⁴ and ICPE.⁵

Background

Across the industry there has been increasing interest in the use of a Common Data Model (CDM) to facilitate systematic analyses of large administrative claims (Claims) and electronic medical records (EMR) databases for real-world evidence generation, and recent research highlights the benefits of this approach.⁶

The concept of the CDM is that data from disparate databases can be transformed into a common data format using consistent assumptions. After transformation, systematic analysis can be performed in a rapid and efficient manner. Because the data has been transformed using consistent rules and analyzed using a single, standardized analysis module written for the CDM, the results across disparate data sources can be efficiently produced and meaningfully compared. This article presents the results of a collaborative analysis of treatment patterns in patients diagnosed with depression across five electronic healthcare databases. Prior to analysis, each of the five databases used in the analysis was transformed into the OMOP CDM format, and then analyzed with a single standardized treatment pattern modular program written to conform to the OMOP CDM. Evidera scientists performed the analysis on one of the databases; the other four were analyzed by scientists at GSK and BMS using licensed observational databases. The parameters used as input to the treatment patterns modular program were identical for each execution. Results of the analysis were compared to better understand similarities and differences across databases and patient populations.

Methods

Source data

Source data came from five distributed sources of HIPAA-compliant patient data, details of which are provided below. Each database was transformed into an OMOP-compliant CDM prior to analysis. Databases were distributed across four physical locations in the U.S. (Pennsylvania, Massachusetts, Connecticut, and North Carolina). Access to the Truven, Pharmetrics, and GE data were covered by data licenses and analyzed independently by the data licensors.

Data sources used were:

• **CCMC - Truven Marketscan**: Commercial Claims and Medicare supplemental claims data. These data are fully integrated, patient-level data containing inpatient, outpatient, drug, laboratory, health risk assessment, and benefit design information from 87 million commercial and 10 million Medicare patients in the most recent five years across the U.S.

- Medco Medco Pharmacy Claims: Commercial Claims data (pharmacy and integrated medical claims) on a subset of 12.7 million patients in the most recent five years across the U.S.
- **GE GE Centricity**: Ambulatory Electronic Medical Record (EMR) data on approximately 13.5 million patients contributed by 30,000 clinicians in 49 states within the U.S.

Table 1: Diagnosis codes used in depression cohort definition

- **PM IMS Pharmetrics**: Commercial Claims data (pharmacy and integrated medical claims) on a subset of approximately 35 million patients in the most recent five years across the U.S.
- **MDCD Truven Medicaid**: Government Medicaid Claims data originating from multiple states within the U.S. on approximately 12 million patients.

Major depression diagnosis codes

296.2 Major depressive disorder, single episode
296.20 Major depressive affective disorder, single episode, unspecified
296.21 Major depressive affective disorder, single episode, mild
296.22 Major depressive affective disorder, single episode, moderate
296.23 Major depressive affective disorder, single episode, severe, without mention of psychotic behavior
296.24 Major depressive affective disorder, single episode, severe, specified as with psychotic behavior
296.25 Major depressive affective disorder, single episode, in partial or unspecified remission
296.26 Major depressive affective disorder, single episode, in full remission
296.3 Major depressive disorder, recurrent episode
296.30 Major depressive affective disorder, recurrent episode, unspecified
296.31 Major depressive affective disorder, recurrent episode, mild
296.32 Major depressive affective disorder, recurrent episode, moderate
296.33 Major depressive affective disorder, recurrent episode, severe, without mention of psychotic behavior
296.34 Major depressive affective disorder, recurrent episode, severe, specified as with psychotic behavior
296.35 Major depressive affective disorder, recurrent episode, in partial or unspecified remission
296.36 Major depressive affective disorder, recurrent episode, in full remission
298.0 Depressive type psychosis
Adjustment disorder with depressed mood
309.0 Adjustment disorder with depressed mood
309.1 Prolonged depressive reaction
Adjustment disorder with mixed anxiety and depressed mood
309.28 Adjustment disorder with mixed anxiety and depressed mood

311 Depressive disorder, not elsewhere classified

Common data model⁷

The standardized format of the OMOP CDM is patientcentric, organizing de-identified patient data into a "Person Timeline" format to facilitate longitudinal analysis. Information included for each person includes a unique identifier, demographic information, and an "observation period" during which healthcare encounters (e.g., conditions, medications, procedures, and visits) are recorded. All healthcare encounters include a start date, as well as an end date where appropriate.

Standardization of the data content is accomplished via a Terminology Dictionary that includes standardized condition and drug vocabularies. ICD-9-CM codes and drug product identifiers (e.g., National Drug Code, Generic Product Identifier) from source data were mapped into the standardized vocabulary.

Cohort definition

Patients, between the ages of 18 to 65, were selected who had a diagnosis of depression between January 1, 2008, and June 30, 2009. Depression was identified using ICD-9-CM codes listed in Table 1. Patients were required to have 180 days of depression-free eligibility prior to their index depression diagnosis.

Analysis

Descriptive statistics of age, gender, and the number and proportion of patients with a qualifying first-line treatment were computed separately for each database/condition combination. "Overall means," e.g., the average across all databases for age, gender, and first-line treatment were calculated as weighted averages of the databasespecific mean values.

Treatment Patterns - Patients who were newly diagnosed (i.e., no depression diagnosis during the 180-day baseline interval) and newly treated (i.e., no baseline antidepressant prescription/use) with a first-line antidepressant within 60 days following index depression diagnosis were identified. First-line medications were categorized into antidepressant drug class (i.e., Selective serotonin reuptake inhibitors (SSRI), Serotonin–norepinephrine reuptake inhibitors (SSRI), Tricyclic antidepressants (TCA), Monoamine oxidase inhibitors (MAOI), and Other). Prescriptions of the same antidepressant occurring within 30 days of each other were combined into one first-line treatment episode. Patients were followed for 365 days following the start of first-line treatment. Medication treatment patterns (definitions below) were identified by examining the data through 30 days following the end of the first-line treatment episode:

- **Continued:** First-line treatment episode continued beyond 365 days.
- **Discontinued:** First-line treatment episode discontinued, with no other antidepressant prescribed within 30 days after discontinuation.
- **Augmented:** A second antidepressant was prescribed during the first-line treatment episode, with at least one additional prescription of the first-line treatment occurring after the prescription for the second antidepressant.
- **Switched:** A second antidepressant was prescribed either during the first-line treatment episode or within 30 days after first-line treatment episode ended. No additional prescriptions for first-line treatment occurred after initiation of the second antidepressant.

Mean and median treatment days were evaluated for each treatment group. In addition, the total number of treatment days occurring during the 365 day follow-up was tabulated. Similarly, the Proportion of Days Covered (PDC) occurring during follow-up was calculated by dividing the number of first-line treatment episode days occurring during the 365-day follow-up period by 365, and multiplying the result by 100. Note that although follow-up for treatment days was limited to 365 days, overlapping prescriptions were not accounted for (i.e., if a refill occurred prior to the end of days' supply from the immediately preceding prescription, the overlap would be counted twice), meaning that treatment days greater than 365 was possible.

Results

All analyses results described below were produced in less than two days (design through analysis completion).

Descriptive information

Demographic characteristics were generally similar across all databases. Overall, approximately two-thirds of subjects were female; only the MDCD data varied from this substantially, having 77.7% females. The average age was 39.2 years; with the MDCD subjects being notably younger (34.8 years) than subjects originating from other data sources (Table 2). The age distributions of data used for the treatment patterns analysis, by database, are presented in Figure 1.

	Overall	ССМС	Medco	GE	РМ	MDCD
Ν	1,391,915	633,755	131,428	132,938	420,905	72,889
% of Total	100.0%	45.5%	9.4%	9.6%	30.2%	5.2%
Female (%)	67.7%	65.6%	63.6%	70.9%	65.0%	77.7%
Age (Mean):	39.2	39.7	41.7	42.1	40.2	34.8

Table 2: Demographic characteristics by data source

Figure 1: Age category by data source, treatment pattern data extract



First-line treatments and treatment patterns

Overall, 17.4% of patients had a qualifying first-line antidepressant treatment; this ranged from 9.6% (Medco) to 29.4% (GE) (Table 3). The type (class) of first-line treatment was very similar across all databases, with SSRIs accounting for 72-75% of all first-line treatments; followed by Other antidepressants (12-17%), SNRIs (8-11%); and TCAs (1-3%) (Table 3). MAOIs represented .01% or less of first-line treatments in each database with too few first-line treatments in any database for meaningful comparison.

Discontinuation was the most common treatment pattern (62.5%), followed by Continuation (17.1%), Switched (12.3%), and Augmentation (8.1%) (Table 3). Overall patterns of discontinuation were consistent across commercial claims (i.e., CCMC, Medco and PM) and government claims (i.e., MDCD) databases (65-69%); whereas the rate of discontinuation estimated from EMR (GE) data was notably lower (45.7%) (Table 3 and Figure 2). The rate of Continuation varied by type of database: Government Claims (5%), Commercial Claims (14-15%), and EMR (32%). The Switching rate was consistent across all database types (12-14%). The Augmentation rate was also consistent across 4 of 5 databases (7-8%), with Government Claims being higher (13%).

Treatment days varied by database, with Government Claims (MDCD) exhibiting the shortest first-line treatment days (112 days [mean], 32 days [median]), and EMR (GE) the longest (414 days [mean], 205 days [median]) (Table 3). Treatment lengths among the Commercial Claims databases (i.e., CCMC, Medco and PM) were very similar with mean values between 193 and 214 days and median values between 85 and 88 days (Table 3). The similarities between commercial claims data, as well as the comparably higher treatment days when calculated from the EMR (GE) data and the lower treatment days when calculated from government claims (MDCD), are maintained when examined by antidepressant class (Figure 3).

The PDC followed a trend similar to that of treatment days with all commercial claims data having very similar PDCs (0.38-0.39), while the EMR (GE) data had the highest PDC (0.58) and the government claims (MDCD) with the lowest (0.26). SNRIs had a slightly higher overall PDC than all other classes, ranging from 0.30-0.53 across all databases (Figure 4). For all individual databases other than GE, the SNRI PDC was the highest of all antidepressant classes. TCA's had the lowest overall PDC, but exhibited a wider variation among databases (0.23-0.60). The TCA PDC was consistent for Claims (0.23-0.28) but significantly higher for EMR (0.60).

Table 3: Characteristics of treatment patternsby data source

	Overall	ссмс	Medco	GE	РМ	MDCD
Qualifying 1st line treatment (%)	17.4%	14.2%	9.6%	29.4%	16.2%	16.5%
Qualifying 1st line treatment (n)	221,802	89,801	12,569	39,062	68,363	12,007
First Line Treatment (%)						
MAOI	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
TCA	1.6%	1.4%	1.9%	1.6%	1.5%	3.3%
SSRI	73.6%	72.9%	72.5%	74.9%	74.3%	72.1%
SNRI	9.9%	10.3%	10.4%	11.1%	8.8%	7.9%
Other	14.9%	15.5%	15.2%	12.4%	15.4%	16.7%
Treatment Pattern (%)						
Discontinued	62.5%	65.3%	65.5%	45.7%	66.7%	69.1%
Continued	17.1%	14.7%	14.9%	32.4%	14.1%	5.3%
Switched	12.3%	12.0%	12.2%	13.9%	11.7%	12.7%
Augmented	8.1%	8.0%	7.4%	8.0%	7.5%	12.9%
TX days (mean)	231	193	214	414	201	112
TX days (med)	104	88	88	205	85	32
PDC	0.41	0.39	0.39	0.58	0.38	0.26



Figure 2: Treatment patterns by data source





Antidepressant Class

Figure 3: Median treatment days by antidepressant class and data source

Figure 4: Proportion of days covered (PDC) by antidepressant class and data source



Discussion

The treatment patterns analysis was conducted on three sets of conceptually similar commercial claims data; therefore the consistent results across the CCMC, Medco and PM data were expected. The disparities seen in some of the Government Claims (MDCD) results (e.g., shorter treatment duration, less continued antidepressant use) may be the result of either population characteristics (e.g., MDCD were generally younger and may represent a subgroup that is less likely to comply with prescribed treatment) and/or different rules for

medical reimbursement. The EMR database exhibited the most inconsistent results (more treated patients, longer treatments), likely reflecting fundamental differences in the underlying reason for data capture in this population (i.e., record of patient medical history as opposed to medical cost reimbursement). Despite these differences, the overall patterns of treatment across disparate databases and populations were strikingly similar, which may reflect the availability of American Psychiatric Association (APA) Treatment Guidelines for Patients with Major Depressive Disorders.⁸

These analyses are subject to common limitations in observational data. Commercial claims data, such as CCMC, Medco and PM are primarily used for administrative purposes, enabling healthcare providers to obtain reimbursement for services provided. As a result, issues such as diagnostic miscoding are possible. Government claims data (MDCD) also are predominately used for administrative purposes, but the populations serviced differ from those of commercial claims. In the EMR (GE) data, diagnostic miscoding, or the absence of diagnostic coding, is potentially greater as these data are not used for reimbursement purposes. Additionally, as it relates to the EMR (GE) data, only prescriptions written is available (whereas prescriptions filled is available in claims data) and days' supply is usually inferred based on National Drug Code (NDC) information. These factors likely lead to the differing treatment patterns observed in the GE data.

Despite these database limitations, we have provided an example of a collaborative analysis of treatment patterns in patients diagnosed with depression, conducted on five disparate observational databases. This research provides a relatively simple, yet applicable illustration of how standardized analytics provides an efficient way of enabling meaningful comparisons across disparate data sources. In addition to the demographic and treatment pattern analyses presented, this general approach can be applied to a variety of retrospective observational analyses (e.g., incidence estimation, health outcomes, drug safety/adverse events, burden of illness, etc.).

The potential benefits of CDM implementation, however, go well beyond individual analysis applications. For example, database epidemiology on rare diseases or orphan drugs is often hindered by inadequate sample size from any single retrospective data source. As such, there has historically been a heavy reliance on patient registries and/or the use of multiple retrospective data sources; both of which result in logistically complicated and costly projects. The ability to efficiently combine data from several disparate data sources using a standardized

format and vocabulary changes this as the CDM enables the easy implementation of either pooled or database stratified analyses (which as we demonstrate above may be necessary due to inherent differences in data capture processes and/or underlying population characteristics that are important for interpreting results produced from each database). Furthermore, the general concept of the CDM can be expanded to multiple, similar patient registries (i.e., multiple registries that focus on similar disease and have many conceptually common data fields), in essence enabling the creation of a "master" registry. The ability to conduct these types of data processing and analyses tasks in a single, standardized manner will certainly minimize (and potentially eliminate) many of the historic limitations inherent in retrospective observational studies.



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Introduction to Disease Simulation: An Emerging Approach to Inform Decision Making

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Introduction

At the heart of quantifying the value of an intervention is the need to understand how its effects measured in a clinical trial will translate to benefits for patients over relevant time horizons (often their remaining lifetime) in a real-world setting. In rare cases, trials may be able to directly inform the required benefit, but in most cases it is necessary to use a mathematical framework — a model — to extrapolate beyond the trial-reported outcomes. This model, at its best, is a full disease simulation, detailed enough to handle the required predictions accurately and carefully validated to ensure its credibility. In this article, we provide an overview of disease simulation including its definition and applications, the types of data that can be integrated, and the communication of results. Our Archimedes Condition-Event (ACE) simulator of Alzheimer's disease (AD) will be used throughout to provide clarifying examples.

What is disease simulation?

A major purpose of a disease simulation is to inform healthcare decision making. It accomplishes this by integrating data on multiple components of a disease in a structure that is sufficiently detailed to address the decision makers' questions. These components include measures that describe the patients' condition, such as their demographic characteristics, treatment history, biomarkers, and patient-reported outcomes; and the resulting probabilities of experiencing events such as disease progression, hospitalization, or death.

A defining feature of disease simulations is that they predict the evolution of the disease components based on the clinical or physiological relationships between them. The focus on clinical and physiologically meaningful relationships affords a clear mechanism for evaluating how well a simulation may perform outside the range of the data used in its development. For example, describing the change in a trial endpoint directly from clinical trial data and extrapolating that change to longer times does not generally require a disease simulation; while the trial data must be extrapolated to longer times, alternate statistical fits are an appropriate way to test how that extrapolation influences the results.

In contrast, evaluating how a treatment might benefit a patient population that was not enrolled in the clinical trial would generally require a disease simulation. Such a question requires an explicit clinical hypothesis of the direct effect of the treatment, how that direct effect would interact with any differences between the trial population, and the population of interest and clinical evidence describing that interaction from outside the trial. A disease simulation is an effective mechanism for integrating this richer set of information and enabling alternate clinical hypotheses regarding the interactions to be tested.

Disease simulation is particularly useful for complex multifactorial conditions with many interacting markers. In AD, for example, understanding the impact of a treatment targeting early biomarkers of disease (e.g., anti-amyloid therapies) requires linking changes in those biomarkers to changes in cognitive, functional and behavioral measures, and those measures, in turn, to outcomes like institutionalization, quality of life, and costs. While there are a variety of data sources and published studies that connect various sets of these, a comprehensive understanding of the pathophysiology and progression of AD has yet to be developed. As such, an AD simulation makes explicit the clinical hypotheses linking the available data and permits evaluation of how specific decisions are influenced by alternate hypotheses.

Disease simulation is particularly useful for complex multifactorial conditions with many interacting markers.

What types of questions does disease simulation address?

By connecting multiple components in a physiologically informed way and generating testable predictions, disease simulation is able to support decision making throughout the development process. One key application of disease simulation is estimating the implications of trial results for submissions to Health Technology Assessment (HTA) groups and payers. When clinical trials report only surrogate endpoints, disease simulation can predict how those will translate to clinical and economic outcomes of interest. At the same time, disease simulation can support forecasting of therapeutic benefit and market potential for different subpopulations. Explicit simulation of various patient populations allows for specific estimates of economic outcomes, such as cost-effectiveness and budget impact. These, in turn, can address the question of how expanding or restricting the indicated population for a treatment influences its costeffectiveness and budget impact.

Before an intervention is ready for market, disease simulation can help evaluate risk and mitigation strategies in planned clinical trials. Outcomes that can be assessed through simulation of a clinical trial include the range of plausible outcomes, the risk of false positives or negatives, and the total duration and cost of a trial. Mitigation strategies that can be considered include changes to selection of population inclusion/exclusion criteria, endpoints, comparators, and duration of follow-up. Simulation of clinical trials under different clinical hypotheses regarding how components of disease are related also enables evaluation of risks associated with uncertainty regarding the true clinical pathology. It is important to emphasize that predicting the potential range of direct effects of a new therapy is, in general, outside the scope of disease simulation and best informed by clinical evidence.

Returning to the example of AD, many current clinical trial programs are evaluating the effects of potentially disease-modifying treatments in patients at the very early stages of disease. Given the incomplete understanding of AD pathophysiology, estimating the probability that a planned trial will yield positive outcomes under various clinical hypotheses provides valuable information that can help the trial designers make choices that minimize the risk of negative outcomes. Another critical question regarding early AD treatment is how its cost-effectiveness and budget impact will vary with the definition of the patient population. This is particularly so with intervention aimed at earlier stages of disease or even in pre-disease conditions. Disease simulation affords a mechanism to quantify both cost-effectiveness and budget impact, with

explicit hypotheses regarding the disease process that can be effectively discussed with, and vetted by, clinical experts.

What types of information can be integrated using disease simulation?

While it is possible to generalize about inputs, it is essential to emphasize the information that should be used for an analysis with a disease simulation is driven by the questions specific to that analysis. Here we consider an analysis that requires simulation of the long-term clinical outcomes implied by short-term clinical trial data on a surrogate endpoint.

To address this question, the scope of the disease simulation must span both the clinical outcomes of interest and the surrogate endpoints. The simulation's scope must include the ability to predict the evolution of the clinical outcomes over long periods of time in a potentially diverse patient population. This scope means the following information should be considered in the simulation: the population being considered (characteristics and epidemiology); the relationships between the measures of disease and outcomes being modeled; the temporal evolution of at least some of those measures and outcomes; and how an intervention impacts the measures.

Direct clinical data, including that from clinical trials, registries, or other observational data sources, is the best source from which this information can be drawn, but there are often gaps in the available data or the clinical understanding of a disease. Clinical expert opinion can help bridge those gaps, but different possibilities should be tested in a disease simulation where feasible for a specific analysis. Additional data is required to bridge to patient outcomes such as institutionalization or healthcare resource utilization.

In our example of an AD disease simulation designed to support the evaluation of an early, disease-modifying intervention, the simulation's scope integrates data on early biomarkers of disease and their connection to cognitive, functional, and behavioral decline. While the biomarker directly impacted by the intervention being considered is key, the complexity of AD and the limited understanding of its true pathophysiology also need to be taken into consideration. Therefore, the appropriate scope includes additional related markers to allow more faithful representation of any clinical trial data and the testing of alternative hypotheses of the disease. In addition, the simulation uses information connecting the early biomarkers to cognitive function and ultimately to patient outcomes. To understand how the population treated influences outcomes, the simulation draws

from data about patient demographics, incidence, and prevalence, supporting consideration of budget impact and clinical trial enrollment.

How can disease simulation inform decision making?

The goal of a disease simulation is to inform decision making. To do so, it is necessary to ensure that the results are not just an appropriate synthesis of the available data, but clinically meaningful and broadly accessible. Disease simulation necessarily incorporates a substantial amount of information, particularly in complex disease areas. This can make it challenging for a decision maker to review a simulation directly or to interpret the results appropriately. It is, therefore, very important to present the design, underlying assumptions and clinical findings of a simulation, including its programming, in a comprehensive but transparent fashion.

One area for focus is the design choices and assumptions regarding how the included disease components are interconnected. These aspects may limit a decision maker's willingness to use the outputs of a simulation. In a well-constructed disease simulation, these assumptions can be tested by running different scenarios, allowing assessment of how the simulation results depend on them. This, in turn, fosters understanding of the credible range of outcomes and the likelihood of particular ones. Beyond this practice, however, the clinical hypotheses represented in the most important assumptions can be reviewed with clinical experts both in direct discussion and via publications.

Clear presentation of how the clinical features of the disease are translated into the simulation structure is important in enabling a disease simulation to be used with confidence. This includes both thorough documentation of the simulation design and accessible programming, which allows the equations to be easily viewed. The programming approach must be carefully considered from the earliest stages of simulation design to afford this clarity, while also enabling the flexibility to test multiple clinical hypotheses across a broad scope.

Finally, a well-designed disease simulation, given its clinically realistic extrapolations, is well-suited to ongoing predictive validation. Such studies can demonstrate the designed scope for a specific disease simulation and the types of questions it is suitable to address. It is essential, however, to emphasize that a significant fraction of the predictions from a disease simulation may ultimately not be borne out — the simulation is only as good as the underlying clinical hypotheses and will evolve over time. Predictive validation, however, provides a clear road map for continued advancement of the simulation and for systematic testing of a set of clinical hypotheses against new data.

Conclusion

Disease simulation is a powerful tool for understanding how an intervention may influence the progression and consequences of a complex disease. The types of questions best addressed by disease simulation, however, require modeling multiple components of a disease and a correspondingly substantial base of information. Appropriately designed disease simulations can provide a consistent framework to effectively inform decision making throughout the development process and subsequently.

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Data Analytics to Enable Data-Driven, Innovative Solutions for Biopharmaceutical Companies: A Brief Look at Selected Methods

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In the era of Big Data and personalized medicine, traditional approaches to data collection, analytics, and visualization are falling short. While it will take some time to separate reality from hype when it comes to the use of technology, it is certain that the healthcare field can learn valuable lessons from other industries in terms of data analytics. Industries such as finance, retail, and engineering have long utilized data analytics successfully to predict stock market dynamics and customer behavior, assess product reliability, solve logistical problems, and predict many key outcomes.

Technology already enabled the digitization and the collection of a vast amount of patient, hospital, prescription, biological, and laboratory data. The volume and complexity of data are posing some practical and logistical challenges for technology regarding the integration of data from different sources (e.g., claims, EMR, patient-reported outcomes) and the real-time use of data. However, what is crucial for any healthcare business going forward is the application of the appropriate methods to these data in order to answer important business questions. Challenges do exist. For example, analysts have to identify relevant indicators hidden in datasets with thousands of variables, and connect the datasets where the predictor and the outcomes exist. Analysts also have to capture potential interaction effects while accounting for nonlinear relationships between variables, and at the same time

face non-traditional data challenges such as unstructured data. As Fawcett and Provost¹ suggest "data, and the adaptability to extract useful knowledge from data, should be regarded as key strategic assets."

In addition to technical/implementation challenges, there will be organizational challenges. For example, there may be a reluctance to embrace unfamiliar and complex methods; decision makers will need proficiency in principles of data-analytics thinking; and, there will be a need for greater collaboration between stakeholders.

Applying data analytics

The discussion about how to use big data has been ongoing for several years, and many players have already acted in order to be ready for the change. Motivated by the Affordable Care Act in the United States, several provider groups and managed care organizations invested in software systems to allow them to integrate and harness the power of data.

Biotechnology and pharmaceutical companies are also adapting to the requirements of the Big Data era. As they obtain more and more data from the R&D process, clinical trials, registries, retailers, patients, and caregivers,² they are also recognizing the importance of data-driven decisions. It is estimated that the use of appropriate data analytic methods can save the pharmaceutical industry \$1 billion annually by eliminating inefficiencies in clinical trial designs.³ For example, data can make developing drugs for rare diseases more economical by enabling pharmaceutical companies to predict patients who can benefit from their products.⁴ Real-world evidence (RWE) can inform the planning of clinical trials by identifying patients who meet inclusion/exclusion criteria; identifying sites and countries that deliver patients on time; estimating the time to enroll patients; and determining the compensation for investigators.⁵ Data analytics can help improve the collection and the quality of RWE to support reimbursement and adoption efforts. Prevalence of conditions required for the clinical trial can be analyzed to assess the feasibility of the trial protocol, for example, by identifying which inclusion criteria are harder to satisfy.

Methods

In Figure 1, some ideas are presented to illustrate how different steps of data analysis, coupled with the right methods, can address different needs of biopharmaceutical companies.

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As seen in Figure 1, there are many methods that can be suitable for addressing different problems, and some of these methods that fall under the machine learning field are yet to reach their full potential in healthcare. (Read more about machine learning in the article Machine Learning: Addressing the Limitations of Real-World Data in this issue of The Evidence Forum). A few of these methods and potential uses are described below.

Cluster analysis relies on a measure of the distance between observations. A population can be grouped in terms of its demographic characteristics, clinical history and health habits to allow healthcare providers to develop appropriate services for different groups. This is one of the key concepts of population health management to identify patient subgroups in terms of their risks. For example, Schuit et al.⁹ use the cluster analysis method to identify whether common lifestyle risk factors in adults form any clusters.

Application Areas	Explore Data	Forecast Outcomes	Simulate Cohorts and Studies
Methods	 Descriptive statistics and epidemiology Patient profiling and identifying subgroups Cluster analysis (of risk factors) Data mining methods 	 Traditional stats and economic analysis Machine learning methods, such as classification and regression trees (CART), boosted logistic regression, AdaBoost, artificial neural networks, etc. 	 Simulated trial comparisons/ matching-adjusted indirect comparisons Propensity scores weighting Time-series analysis and forecasting
Solutions	 Identify high risk patient subgroups Identify patients who are likely to respond to certain treatments Identify which treatment is appropriate for a patient profile Inform protocol and clinical site selection Monitor population health/chronic disease management Identify clinical and economic burden of disease Inform product development and evidence generation plans Inform market size and pricing decisions 	 Quantify and compare short- and long-term clinical and economic value of interventions to drive adoption Inform trial designs, collection and design of patient-reported outcomes Compare treatment decisions and pathways Identify potential safety/risk issues, predict future events Inform commercialization plans Predict infection rates in hospitals Predict re-order rates for a product or hospital re-admission rates for a patient 	 Inform clinical trial designs, patient registries, Risk Evaluation and Mitigation Strategies Identify safety issues by using time series to monitor adverse events Enhance/link other real-world evidence to inform decisions in other regions Inform clinical decision making based on forecasted risk based on patient attributes Test regulatory and reimbursement requirements under different scenarios Design patient engagement and monitoring strategy

Classification and regression trees (CART) separate the dataset into subgroups according to a set of *if-then* rules based on a set of explanatory variables; it estimates the response variable in each subgroup and then predicts response values for new observations based on which subgroup they fall into. This method offers the benefit of easy interpretation of results. An example application of classification and regression trees is the prediction of infections among hospitalized patients.⁶

Logistic regression is commonly used to assign probabilities to a response variable based on observed characteristics. A method that may greatly improve the predictive power of a logistic regression is **AdaBoost algorithm**.⁷ An initial logistic model is fitted to the data, and the observations that are misclassified are then weighted more than the observations that are correctly classified. Then a second logistic regression is fitted to weighted observations, and the process is repeated a predetermined number of times. Each logistic model also gets a weight that is a function of how well it predicted the previously misclassified observations. The final model classifies new observations according to the majority vote of weighted logistic models, improving the accuracy of predictions relative to a more complicated single logistic model. Another way to improve the logistic regression is the **boosted logistic regression**.⁸ The boosting algorithm increases the likelihood function of the logistic model by iteratively fitting regression trees to the error terms from the logistic regression and adding the regression trees to the linear term in the likelihood function. Each new regression tree is fitted to the residuals from the model that includes previous regression trees, and this approach increases the accuracy of the predictions. The boosted logistic regression does not require the analyst to specify potential interactions or nonlinear effects.

This article presents only a small sample of available methods. Regardless of the methods used, without the guidance of experts, extracting knowledge from data and using this knowledge to inform business decisions will not be possible. Predictive analytics, when implemented by those with the necessary expertise, can lead to better decision making, and ultimately drive improvements in healthcare.

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Machine Learning: Addressing the Limitations of Real-World Data

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The field of retrospective observational studies (ROS) and real-world data (RWD) is undergoing fast-paced development. The increase in available data sources has been accompanied by a rapid methodological evolution to address problems commonly encountered in RWD studies. For example, problems may include the evidence being fragmented across multiple datasets; the target population being inconsistently identified or present in the data but undiagnosed; or the information only being available in free-text elements of the data source. Here, we describe how an approach called machine learning can help you solve these types of problems and get the most out of your data.

What is machine learning?

At its heart, machine learning is an algorithmic approach to extract meaning from data. Although you may not have heard of it, you encounter machine learning every day without realizing it. It is used by email providers to filter spam from your email, by banks to prevent credit card fraud, and by companies like Amazon, Google, and Facebook to present content personalized to your interests. In short, machine learning permeates everyday life.

Machine learning originated from multiple fields, including classical statistics, computer science, artificial intelligence, and data mining. It is most often compared with classical statistics, but there are a few key differences worth noting. Classical statistics generally assumes the data is generated by an underlying probability model. It is largely concerned with hypothesis testing, goodness of fit testing, and inference from historical data. In contrast, machine learning assumes the data is generated by an unknown mechanism and is largely concerned with learning the patterns within data to make accurate predictions.

Machine learning methods

Although machine learning is ubiquitous outside of biomedical fields, it has not yet seen the same level of adoption in the healthcare industry. However, an increase in the use of machine learning is being seen as the volume and variety of data grows.

Machine learning methods are well-suited to large datasets that incorporate a wide variety of data types, including unstructured data like text, CT scans, or genomic data. There are many different machine learning techniques with catchy and enigmatic names: classification and regression tree (CART), random forest, AdaBoost, support vector machines (SVM), neural nets, Bayesian networks, and C4.5 are frequently used. Some techniques excel in specialized applications; other times choosing the right technique is more a matter of art than science.

Within the biomedical field, there is a great need for transparent and human interpretable output. Decision makers must trust the model to act on its results. In this scenario, an easy-to-explain method such as a decision tree may be preferable to an opaque method such as a neural network, even if the decision tree is less powerful. Decision trees produce visible rules that are easy to follow and understand, meaning people like front-line clinicians can quickly apply it and communicate its results.

Machine learning methods are well-suited to large datasets that incorporate a wide variety of data types...

Use cases

Machine learning has many applications in the healthcare industry. In a straightforward translation of traditional business analytics, machine learning can be used to predict which patients will discontinue a drug for a chronic disease. A company can then take action to reduce patient "churn" and increase revenue.

Another important area for machine learning is improving diagnoses and predicting disease outcomes. It has been used for the early detection of Alzheimer's disease¹ and can improve the accuracy of cancer outcome predictions by 15–20%.²

Machine learning is an ideal approach to solve problems presented by retrospective and realworld data. For instance, in a recent study done at Evidera, the prevalence of post-stroke spasticity (PSS) was observed to be as low as 1% in clinical practice research datalink (CPRD) data. This observation was well below the 20–30% prevalence of PSS in the published literature. The speculation was that not all stroke patients that developed spasticity were given a diagnostic code for spasticity by their primary care physician. Such an underreporting of PSS in CPRD data would make any future studies of costs of care subject to bias.

If you proceeded to conduct this study using the limited number of PSS patient records, your results would be biased because the few cases identified in the data were likely to be a subpopulation of the most severe cases. To overcome this limitation, we used our expertise in machine learning to identify a previously undiagnosed population of PSS patients in the CPRD dataset. With the help of key opinion leaders who helped create a list of treatments frequently used for PSS, we boosted the sample size from 665 to nearly 4,000 PSS patients and reduced the bias in results when compared to conducting analyses only on the 665 patients who received a diagnostic code. This study is a perfect example of how machine learning can overcome the perceived limitations of RWD and yield considerable benefits.

Limitations

Machine learning techniques can be immensely powerful, but they require careful and expert application. Special care must be taken to avoid "overfitting," in which the model produces highly accurate predictions for the data it was trained on but is completely ineffective and inaccurate when used to make predictions on new data. Overfitting is one of the most frequent mistakes seen in studies using these techniques.

Machine learning is an ideal approach to solve problems presented by retrospective and real-world data.

Conclusion

The success of machine learning techniques led to its rapid and widespread adoption across a diverse range of fields and disciplines. Since skills and expertise in machine learning are still rare in the healthcare industry, few realize that it can be used to solve many of the problems frequently presented by RWD studies. As the benefits of machine learning are better understood, we are likely to see a large increase in its usage over the coming years.

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Multi-Criteria Decision Analysis: When and How to Implement to Meet Stakeholder Demands

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Introduction

In the June 2012 and November 2012 issues of this newsletter, Evidera published articles highlighting the role that multi-criteria decision analysis (MCDA) could potentially play in healthcare decision making. Since then, much work has been done to develop and apply MCDA methods in this area.

While some companies are using MCDA to support their product development and value communication, many others have limited knowledge of MCDA or may only know the term and are still unsure how it will impact what they do. They are interested in practical advice on what, when, and how they should be using MCDA.

This article intends to address some of the questions frequently asked by our clients, including:

- 1. What is MCDA?
- 2. Is MCDA merely of academic interest or is it being applied by decision makers?
- 3. When should I implement MCDA?
- 4. How should I implement MCDA? Is there best practice guidance that I should follow?

What is MCDA?

MCDA is a collection of analytical methods used to support decision making in the context of multiple, often conflicting objectives. While MCDA encompasses a multitude of methods, there are several steps that are common to many of these methods¹ (Figure 1).

The combination of these steps has been referred to as "... a formalization of common sense for decision problems which are too complex for informal use of common sense."²

Put another way, MCDA provides a framework for breaking down a complex decision into more manageable components; defining and understanding the relationship between these components; measuring each component; and then combining them to identify solutions. In this way, MCDA enables decision makers to think through a problem systematically and minimize the use of heuristics, as often happens when humans are faced with complex problems. This brings a number of benefits:

- Ensuring that all relevant criteria are considered by decision makers
- Providing a transparent synthesis of both quantitative and qualitative evidence on performance of options against criteria



Figure 1: Steps common to many MCDAs

- Quantifying stakeholders' priorities and preferences, an element of decision problems that is often not addressed systematically
- Fostering a shared understanding of a decision problem and identifying areas of important disagreement
- Forming a transparent link between judgments and decisions

Is MCDA merely of academic interest or is it being applied by decision makers?

While healthcare has been relatively slow in realizing the value of MCDA, recent years have seen payers and regulators consult on, pilot, and employ MCDA to support their decision making. Figure 2 illustrates the range of ways in which MCDA is being integrated into healthcare decision making. A number of observations can be drawn from the examples shown in Figure 2.

Decision types: MCDA is being used to support a range of decision makers, including regulators and national and regional HTA agencies.

Method: Even within decision types, the MCDA methods adopted by decision makers display important variation. For instance, the Institute for Quality and Efficiency in Healthcare (IQWiG) has suggested the use of the analytical hierarchy process (AHP) or discrete choice experiments (DCE) to generate criteria weights,^{3,4} while much more simple, direct weighting methods are employed in Hungary⁵ and the Lombardy region.⁶

Figure 2: Examples of the use of MCDA by healthcare decision makers



These examples also point to how MCDA is being employed by HTA agencies despite the concerns of critics. For instance, the discussion of the role of MCDA in healthcare often focuses on its use as a replacement for cost-utility analysis. In this context critics point to the difficulties of constructing a willingness-to-pay threshold for a multi-dimensional notion of value such as captured in an MCDA. The examples summarized in Figure 2 point to alternative ways that MCDA can support HTA, including:

- MCDA can be seen as a way to better structure decisionmaking committees' consideration of evidence across multiple criteria, as is the case in Hungary and the Lombardy region in Italy.
- MCDA can be used to generate aggregate benefit estimates with which to construct efficiency frontiers — graphical representations of the interventions that provide the most value for any given level of investment — as has been proposed by IQWiG.

When should I implement MCDA?

The focus of this article has so far been on the use of MCDA at launch — as part of either regulatory or reimbursement decisions. However, industry's use of MCDA extends beyond this. Figure 3 summarizes the stages of the product development process where MCDA is currently employed by industry, including:

Pre-launch: It important to incorporate MCDA early in the product development process. This not only ensures that evidence generation focuses on those data required to inform the MCDA undertaken later in the development process, but MCDA can also support internal decisions about which molecules, target product profiles, or evidence generation strategies in which to invest.

Post launch: Subsequent to launch, industry uses MCDA to help communicate value messages to clinicians and payers, with its ability to synthesize multiple value messages into a single quantitative estimate of overall value.

A good example of the early use of MCDA for project prioritization is the Allergan experience.⁷ Allergan commissioned an MCDA to prioritize 52 potential investments across five therapy areas. An efficiency frontier approach was adopted, expressing the value for money of investments based on cost and a multidimensional measure of benefit. An MCDA was conducted to estimate the benefit of investments based on four criteria: 1) whether investments addressed unmet medical need; 2) whether the investment protected existing franchises; 3) the probability that the investment would prove successful; and, 4) the contribution of the investment to the strategic goal of developing a specialty pharmaceutical company.

The performance of the investment against these criteria was measured by the marketing and product development teams. A two-day workshop was held to elicit stakeholders' preferences for criteria and to review and interpret the results of the MCDA. Participants were positive about this experience. One noted that the MCDA was "the first time I have seen all our projects on one display," and others said that it stimulated teams to re-think strategies and motivated them to seek products that would provide better value.



Figure 3: MCDA is applied throughout the process of product development

How should I implement MCDA? Is there best practice guidance that I should follow?

The diversity of approaches to implementing MCDA (see Marsh et al., 2014⁸) creates challenges for industry. Clients often come to Evidera with a range of questions, such as: Which criteria should we include in our MCDA? and Which scoring and weighting techniques should we adopt? Figure 4 illustrates some of the diversity of methods that are used in MCDA, just considering weighting methods. This divides the methods into four types:

- 1. **Ranking:** Stakeholders are asked to rank criteria, and assumptions are made to translate ranks into weights.
- Direct weighting: Stakeholders provide their assessment of the importance of criteria by, for instance, giving each criteria a weight of between 1 and 5, where 1 denotes lowest weight and 5 denotes the highest (such as in some versions of EVIDEM⁹), or by allocating 100 points across the criteria in a manner that reflects their relative importance.
- 3. **Pairwise comparison:** Stakeholders compare pairs of criteria, indicating their relative importance. For instance, the Analytical Hierarchy Process asked stakeholders to rate pairs of criteria on a 9-point scale, where 1 indicates the criteria are equally important and 9 indicates that one criteria is extremely more important than the other.
- 4. Multi-attribute utility theory (MAUT)-based methods: Stakeholders' preferences are elicited in a manner that corresponds with the axioms of utility theory — transitivity, completeness, independence. For instance, Discrete Choice Experiments provide respondents with choices between hypothetical interventions, from which weights are inferred.

While not intending to be comprehensive, Figure 4 already illustrates the diversity of techniques available.

The non-health literature contains frameworks that are useful starting points for understanding the differences between MCDA methods, as for example, in Guitouni and Martel, 1998.¹⁰ These emphasize factors such as the required transparency and meaning of weights; the nature of decision makers' objectives; cognitive burden on participants; the opportunity for stakeholder learning processes; and, cost and time. Evidera would agree with the conclusion often drawn by authors that there is no "best" MCDA method. Rather the appropriate approach should be determined based on decision makers' objectives, the stakeholders who are providing preferences, and the level of precision called for. In other words, a balance needs to be struck between the cognitive effort placed on the decision makers and the quality of the models' outputs, given the stakes involved in the resulting decision.

Further work is required to provide guidance to those working in healthcare on selecting appropriate MCDA approaches. Work to develop such guidance is underway. In particular, the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) recently established the "Multi-criteria Decision Analysis in Health Care Decision Making Emerging Good Practices Task Force." It aims to help define MCDA and provide best practice guidance for conducting MCDA to aid healthcare decision making. Evidera is delighted to be involved in this important initiative and looks forward to sharing initial guidance during the ISPOR Annual Meeting being held in Philadelphia, May 16-20, 2015.





AHP = Analytical Hierarchy Process

DCE = Discrete Choice Experiment

EVIDEM = Evidence and Value: Impact on Decision Making

 \mathbf{SG} = Standard Gamble

TTO = Time Trade-off

Conclusion

Since our earlier articles written about MCDA in this publication, much work has been done to develop and apply MCDA methods to support healthcare decision making. These efforts will help bring the benefits of MCDA — transparency, rigor, consistency, and accountability — to healthcare decision making.

Recent experiences implementing MCDA in healthcare also point to a number of lessons for industry:

- 1. MCDA should be applied throughout the production development process to support investment decisions, submissions and value communication.
- MCDA includes a diversity of methods, and it is not possible to identify a "best" approach. Rather, it is important that researchers are aware of the different demands of decision makers for MCDA, as well as the insights that are generated from ongoing efforts to generate best practice guidelines for healthcare.



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What's in a Name? Systematic and Non-Systematic Literature Reviews, and Why the Distinction Matters

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At Evidera, we routinely have conversations with external colleagues who would like our help in gathering publicly available information to answer research questions, inform business decisions, support submissions to external authorities, or provide inputs into other research efforts such as economic analyses. The scientific literature is a rich source of information that can guide healthcare research and decision making, and a literature review is often a cost-effective and time-efficient approach to gather evidence.

In our experience, different people may have quite different types of studies in mind when they use terms

such as "systematic literature review." At a minimum, this range of understanding can result in confusion and unclear expectations and, in some cases, it could even impact the success of the literature review as a standalone project or the success of associated downstream activities such as qualitative or quantitative research or external submissions.

The accompanying table outlines some common types of literature and informational reviews, their typical methodology and objectives, and how they might be used to inform other efforts.

Type of	Definition	Methodologies	Objectives and
Review		Employed	Typical Applications
Systematic literature review (SLR)	A scientific study designed to address a specific research question by comprehensively collecting all the information available on a topic that is defined at the outset by absolute inclusion and exclusion criteria. Considered the "gold standard" for evidence assessment. When appropriate, this gold- standard approach may be adapted to produce a more manageable scope while retaining elements that ensure rigor and minimize bias in the identification of relevant literature (e.g., use of a protocol, systematic search, and screening). Such an approach is sometimes called a structured review.	 Follow established guidelines set down by authorities such as the Institute of Medicine and the Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) Statement.¹ Typically involves searching multiple, predefined electronic databases and grey literature sources. Selection criteria define topic areas as well as characteristics such as publication dates, the languages in which articles are published, and whether articles describe only human subjects. The search and screening protocol is reported in the methods section of the report, along with a PRISMA diagram, a flowchart showing the number of — and reasons for — articles being identified and excluded at each step of the process. 	Considered the optimal type of literature review for publication (particularly in higher tier medical journals) and conference presentations. Required for many payer submissions and other types of formal documentation. Findings can be used to conduct a classical meta-analysis or network meta-analysis (indirect/mixed treatment comparison); may also be used to provide inputs for economic models. May be qualitative, e.g., to assess burden of illness; epidemiology; clinical, economic, and humanistic outcomes; or treatment patterns. This information can be used to guide evidence generation strategies and clinical development programs.

Type of Review	Definition	Methodologies Employed	Objectives and Typical Applications
Targeted literature review Also called a "focused literature review"	A non-systematic literature review that is meant to be an informative, rather than all-encompassing, review of the literature on a topic. Generally takes an in-depth but not systematic approach to a specific research question.	Largely based on a knowledgeable selection of current, high-quality articles on the topic of interest. May or may not follow a predefined protocol.	Guide strategy and support evidence-based decision making within a product team. Help to identify trends and better understand the current state of a field. Generally the preferred approach for populating disease and treatment background sections of a dossier or for identifying model inputs. Can be published, but generally appears in lower tier journals than systematic literature reviews.
HTA review	A comprehensive review of health technology assessments (HTAs) regarding a medical intervention, product, or therapeutic area.	Generally, a defined list of HTA sources and sites are searched using a fairly broad set of search terms relating to the subject matter. The resulting HTA reports are screened for relevance.	Understand past payer decisions and feedback on an area of interest. Inform evidence generation and clinical development plans. Identify potential payer concerns and proactively develop evidence- based responses.
Landscape review or disease area strategy report	A rapid review of key topics of interest relating to a therapeutic area, including but not limited to burden, unmet need, competitive landscape, payer perspectives, regulatory considerations, and data gaps.	Integrates evidence from literature, pricing and reimbursement sources, HTAs, and other public sources and, in some cases, proprietary sources such as payer and provider research, and advisory boards.	May be used to inform decision making on in-licensing opportunities or new development programs. Provide background evidence for a preliminary framework value proposition, value demonstration plan, and/or payer research program.
Gap analysis	An analysis of topic areas in which evidence is sparse or nonexistent, often conducted as part of a literature review and/or evidence generation plan.	Therapeutic area experts typically analyze outputs of a targeted or systematic literature review and identify gaps, and then conduct follow-up searching to confirm the lack of evidence.	Anticipate potential concerns that may arise from payers. Inform an evidence generation plan.

What type of review would best suit your needs?

When considering what type of review would best meet your research and business objectives, ask yourself and your colleagues:

- What is the evidence need, and which specific research questions do we want to answer?
- How much time and resources can we commit to this effort?
- How quickly do we need the research findings to be available?
- Who are the internal and/or external audiences for this review, and do they have specific expectations or stipulations about how it will be conducted?

- Are there established guidelines governing how this type of review should be conducted?
- Do we intend to publish our findings?
- Would this review be useful to other work streams within our organization? If so, do their requirements differ from ours?

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Assessing the Burden of Care from the Perspective of Healthcare Professionals

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The burden of care for a disease includes many different cost elements, some of which are easier to measure than others. For example, the costs incurred by a healthcare provider for an episode of care include not only staff wages and supply costs, but also opportunity costs of capital, training, and liability that are more difficult to attribute. Furthermore, many cost elements are not typically recorded in an existing data source, and researchers may need to turn to a primary data collection methodology. One approach is to query healthcare professionals (HCPs) who are responsible for delivery and management of care to the patient. This can yield rich data that is tailored and streamlined to answer the specific research questions of interest.

We are currently conducting a study that assesses the burden of care for patients with schizophrenia and bipolar I disorder who present at emergency departments or psychiatric emergency service units in an agitated state. Many of these patients can be quite agitated and treatment can have diverse and costly effects, such as delays in caring for other patients, loss of revenue due to occupied beds and ambulance diversion, staff injuries and frustration, patient complications due to needle injuries, and property damage.

We elected to assess this burden by interviewing and surveying HCPs who were experienced in caring for agitated patients with schizophrenia and bipolar I disorder. We first conducted qualitative interviews to learn more about the issues and inform the development of a quantitative provider survey. We are now in the process of surveying via the Web 200 HCPs experienced in caring for the target patient population. At present the fieldwork is ongoing for this study.

Qualitative interviews

One-on-one telephone interviews were conducted with 10 HCPs (two emergency medicine physicians, two registered nurses (RN), two hospital administrators and one each of the following: psychiatrist, licensed practical nurse (LPN), hospital aide, and social worker) in the United States. The interviews contained openended questions to understand the HCPs' experiences caring for patients with agitation and schizophrenia or bipolar I disorder. The results from the qualitative interviews informed the development of the Web survey.

Web survey

A cross-sectional Web survey of 200 HCPs, including emergency medicine physicians, psychiatrists, RNs, LPNs, hospital aides, social workers, and hospital administrators is being conducted. The survey includes multiple choice questions, rating questions, ranking exercises, and open-ended questions to assess the burden of treating patients, including use of restraints, isolation, boarding, length of stay, staff abuse and injury, and direct costs. For most questions, participants are asked to think about their "most recent patient with agitation and schizophrenia or bipolar I disorder."

HCPs are recruited through an external partner that specializes in clinician recruitment via its proprietary database. Potential participants who meet the screening criteria are emailed an invitation to participate in the study. The email contains information about the survey purpose and a unique link to the survey website. Interested participants click on the unique link and enter the survey website. Recruitment is conducted to ensure geographic diversity.



The Web survey consists of sections on patient management, boarding and length of stay, staff abuse and injury, emotional impact, and demographics. The administrators completed additional items on staff training.

As mentioned above, the purpose of the survey is to obtain information on the real-world burden of treating patients with schizophrenia and bipolar I disorder who are agitated. As such, the survey includes items to address the full burden of care. For example, in the patient management section, items ask about the methods used to decrease the patient's agitation and the sequelae of such methods, such as needle injuries, bruising, and over-sedation. Data on the length of time and number and type of staff required to manage the patients are also collected. In addition, there are several items with visual analogue scales for respondents to rate the emotional impact of caring for patients with schizophrenia and bipolar I disorder who are agitated. For example, during the qualitative interviews, a common sentiment among the HCPs was a high level of frustration when caring for these patients, so the following item is included in the survey:

Please rate your **level of frustration** while caring for your most recent agitated patient with schizophrenia or bipolar I disorder.



Staff taking care of these agitated patients can experience abuse and injury requiring medical attention, including pharmacological treatment and psychological counseling, and resulting in productivity loss in the form of days absent from work. This important information is also collected in the HCP survey.

This study aims to bridge the wide data gap in understanding the comprehensive cost of caring for agitated patients with schizophrenia or bipolar I disorder in the emergency department. The Web survey collects information on many aspects of a healthcare provider's burden that are not contained in existing data sources such as claims data and medical chart data. When assessing the burden of care, researchers should consider utilizing the methodology outlined here to assess the "ghost" costs that are often forgotten and are difficult to assess, leading to underestimation of the real burden of care.

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The COA Qualification Process: Where Are We Now and What Have We Learned?

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With the release of the final U.S. Food and Drug Administration (FDA) guidance for the qualification process in January 2014 titled *Qualification Process for Drug Development Tools*,¹ a number of qualification projects are actively underway for a wide variety of conditions, including ulcerative colitis, Crohn's disease, asthma, cystic fibrosis, functional dyspepsia, gastroparesis, and non-small cell lung cancer, to name just a few. Currently, there are 86 Drug Development Tool (DDT) projects in various stages within the qualification program, of which 55 are Clinical Outcome Assessments (COAs).²

The qualification process is intended to expedite the growth of publicly available DDTs for a specific context of use in clinical trials to expedite drug development and regulatory review. It is designed to encourage scientific collaboration from multiple sponsors to increase efficiencies and reduce the cost burden associated with developing a COA. To date, however, only one COA, The EXAcerbations of Chronic pulmonary disease Tool (EXACT), submitted by Evidera, has been issued qualification.³

Evidera is currently involved in a number of qualification projects across various therapeutic areas, including gastroenterology (ulcerative colitis, Crohn's disease, and gastroparesis), infectious diseases, pulmonary/ respiratory diseases, and pharmacology/toxicology. Given all this recent activity, it is time to reflect on the current qualification process and address some of the advantages and challenges that the pharmaceutical industry faces with this process, specific to COA development, and examine how these challenges might be mitigated to maximize future qualification work for instrument development.

The qualification process

Since the release of the guidance in 2014, the process has been slightly modified to increase efficiency and obtain earlier qualification. The COA wheel and spokes diagram (Table 1) depicts the key components of instrument development and the points at which qualification may occur.²

Spoke I corresponds to the initial stage of the process, whereby a letter of intent is submitted, addressing the concept of interest that the instrument seeks to measure (e.g., specific symptom presence or severity, limitations in daily activities); its proposed clinical context of use for which qualification is being sought (target population, study design, endpoint positioning); and rationale for use in drug development (addressing an important unmet need).

Spoke II encompasses the qualitative phase of instrument development up through the evaluation of content validity, while Spoke III includes cross-sectional evaluations to examine the structure (domains) of the measure, develop a scoring system, and evaluate psychometric properties of reliability and construct validity. At this point in the process, the consortium can elect to submit the available evidence for COA qualification. Qualification at this time will enable the COA to be used as an exploratory endpoint in clinical trials, for the purpose of collecting longitudinal data to assess ability to detect change, identify responder definition(s), and provide guidelines for interpretation of treatment benefit (Spoke IV). Once all measurement properties have been adequately examined, all evidence will be reviewed to support COA qualification for use as primary or secondary endpoints of effectiveness.

Table 1. COA qualification spokes and wheel diagram



Advantages of the qualification process

Based on Evidera's experience with qualification projects, which includes working with as few as two sponsors for COA development as well as with larger working groups such as the COPD Foundation,⁴ several key advantages of the qualification process were identified related to increased scientific robustness of instrument development, ongoing engagement with the FDA, and the potential for reduced costs to individual sponsors for their overall drug development programs.

Scientific robustness

The collaboration of multiple industry leaders lends itself to the increased scientific robustness of studies conducted to support the COA qualification. Generally, consortiums are set up to include industry sponsors who work in collaboration with a steering committee, represented by individuals who have clinical knowledge as well as those with expertise in instrument development and measurement. With pooled resources, both intellectual and monetary, the collaborative interaction and sharing of ideas has the added advantage of advancing the science of the therapeutic area itself.

FDA engagement

The FDA's Center for Drug Evaluation and Research (CDER) emphasizes that early and continued interactions with the FDA during the instrument development process are not only encouraged, but seen as critical to the success of the program.² The COA Qualification Review Team (QRT) is comprised of representatives from three groups: The Study Endpoints Team (from The Study Endpoints and Labeling Development [SEALD] staff), the appropriate review division(s), and the Office of Biostatistics.

While formal decisions at key points in the qualification process are provided in written format by the QRT, working groups generally have relatively easy access to the QRT, typically via teleconferences. These informal meetings are meant to be collaborative in nature and may provide sponsors with key insights into the "thinking" of the FDA as well as provide an opportunity to get clarification and discuss any outstanding issues at key junctures in the COA development program to keep the process moving forward in an efficient manner.

Cost

It is generally assumed that collaboration with multiple sponsors will reduce the overall costs related to the development of COAs for individual sponsors compared to costs associated with developing product-specific COAs within the context of individual drug development programs. However, the potential to reduce costs is often contingent on the number of sponsors involved in the consortia and the complexity of the overall project.

It is also important to keep in mind that obtaining COA qualification generally takes a number of years, with obvious implications for cost. While the cost related to qualification work can seem rather high to individual sponsors, it is important to note that overall the costs may be less (or equal) to costs associated with individual drug programs, especially when one considers the possibility that a drug-specific COA may not be accepted by the FDA as a primary or secondary endpoint after resources have been expended for its development.

Disadvantages of the qualification process FDA review timeline

There isn't one. The QRT is not obligated, nor held accountable, to review qualification submissions on a specified timetable. The QRT is essentially a volunteer group with the legal obligation and priority for review centered on the traditional investigational new drug/ new drug application (IND/NDA) approval process for drug development as set forth by the 1992 Prescription Drug User Fee Act (PDUFA). That said, CDER continues to encourage instrument development and qualification. While qualification reviews submitted by Evidera were essentially put on hold during 2014 due in large part to a backlog of PDUFA obligations and limited staff at SEALD, recent communications with the QRT indicate that it is fully staffed and committed to timely review.

Consensus

Achieving consensus among multiple industry sponsors can be challenging. At the outset, CDER requests a welldefined COA concept (i.e., proposed instrument) and specific context of use to ensure that, once qualified, the instrument is fit for purpose to measure a primary or secondary endpoint in a specific clinical context of use. While the context of use may be modified or expanded over time as additional data are collected, the initial context of use (and other key components) is critical to CDER's decision to accept the DDT request and advance to the consultation and advice phase of qualification. Given the extended timelines associated with the qualification process, there also is likely to be a change in sponsor representation, causing the working group to revisit issues that were previously agreed upon.

Competing timelines and priorities

A number of qualification projects operate within a precompetitive framework (i.e., independent of specific drug issues), including PRO Consortia projects within the Critical Path Institute (C-PATH).⁵ However, a number of smaller consortia groups have been formed to develop COAs within the context of the qualification process for use in drug development programs. Industry sponsor members who have come together independently to form a consortium and participate in the qualification program generally have different drug development timeline priorities that may impact decisions and collaboration.

Given the lengthy timeline associated with qualification, attrition may occur, whereby industry members may elect to leave the consortium before qualification, due to any number of changes within the respective companies (e.g., change in drug development priorities, failed molecule, change in company staffing, etc.).

Administrative logistics

The administrative logistics cannot be overstated. The legal process for contracting between industry sponsor members can take up to a year — delaying project commencement. Internal processes of each sponsor member must also be taken into account to allow for appropriate review of all essential documents within each organization. In addition, time must be allowed for the regulatory staff review required within each company.

...the qualification process has the potential to increase efficiencies and reduce costs related to the COA development...

Mitigating challenges and moving forward

While the qualification process has the potential to increase efficiencies and reduce costs related to the COA development, there is little doubt that consortiums have faced a number of challenges during the past few years. It is unlikely that the administrative logistic challenges will change in the short term, although legal issues and contracting may become less cumbersome in the future as pharmaceutical legal departments become more familiar with consortium collaboration. There are, however, several ways to mitigate some of the other identified challenges to improve the current qualification process.

Managing expectations

It is important to manage the expectations of industry sponsors when forming a consortium. First and foremost, members should be aware that the process for developing COAs for gualification is "a marathon and not a sprint," with timelines that could span several years or more. With that in mind, sponsors are encouraged to pursue the traditional drug development approval path in parallel to the consortium activities. In addition, guidelines for consensus building need to be addressed, so that issues agreed upon are not revisited. Sponsors also need to keep in mind that all qualified COAs will be made publicly available (albeit through licensing agreements) for others (i.e., competitors) to use in their own drug development programs. Industry sponsors need to strategically assess their own needs and timelines, as they progress through the qualification process.

Sponsors with similar goals

Especially for smaller consortia groups, it is important to include industry members with similar objectives for COA development and similar timelines. The qualification process will proceed much faster and more smoothly if sponsors are able to develop a focused context of use for which the proposed COA would be used. As stated above, the context of use can always be updated and modified with additional data collection and re-submitted to the QRT at a later date.

Scientific dissemination

Have a plan for scientific dissemination to demonstrate short-term accomplishments. The qualification process for COAs can take years from inception to the issuance of qualification. Presenting posters and submitting manuscripts not only demonstrate to internal stakeholders that instrument development is progressing, but it can be beneficial in obtaining important "buy-in" from others in the industry or increasing interest among additional sponsors to join the consortium.

Summary

CDER continues to encourage instrument development and qualification, especially in areas with unmet needs. The qualification process is fairly new and continues to evolve as more and more industry sponsors, academics and patient advocacy groups get involved. While there are certainly challenges, most of these can be mitigated as lessons are learned to improve the overall process.

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Market Access of Orphan Drugs in China

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Overview

Market access of orphan drugs in China involves many challenges, including the absence of official legislation for orphan diseases; the lack of impactful incentives for manufacturers to develop orphan drugs; and limited resources available for funding high-cost orphan drugs. This report is based on secondary research and primary research from interviewing payers (national, regional, and local) and key opinion leaders, and provides insights to the challenges faced by manufacturers and the actions that manufacturers can take to support the market access of orphan drugs in China in the short, medium, and long term.

Market access environment for orphan drugs in china

Absence of official legislation

Lack of official definition of orphan diseases in China

Compared to other Asian markets and major Western markets, China's policies around orphan conditions and drugs are not well developed. There is no official definition of the prevalence of orphan diseases that is recognized by the Chinese government.¹

Among clinical experts, there is a consensus on a working definition of orphan disease emerging. In a Clinical Expert Seminar on the Definition of Rare Diseases held in 2010, orphan disease is defined as having a prevalence of less than 1 patient per 500,000 people or a neonatal morbidity of less than 1 patient per 10,000 people, which is more restrictive than the World Health Organization (WHO) definition of 0.65-1 patients per 1,000 people.^{1,2}

First treatment centers established to better understand orphan diseases

Faced with the challenge of serving the world's largest orphan disease population, China launched its first pilot project in 2013 to frame the health policy situation and to better understand the epidemiology and treatment guidelines for 20 rare diseases.¹

The focus of this pilot program is to develop medical guidelines and clinical pathways for rare diseases; establish a rare disease patient registry and data repository system; and promote molecular testing for rare genetic disorders. It also aims to build close links among collaborative networks: clinicians on the front lines of basic medical services institutions and rare disease patient organizations. A national network including about 100 provincial or municipal medical centers has been established in order to enable collaboration on rare diseases across China.¹

Absence of impactful incentives

Lack of enforced fast track approval channel

The market authorization approval process in China is generally quite lengthy. After the application is submitted by manufacturers, it can take up to a year to get an approval from the State Food and Drug Administration (SFDA) and the Center for Drug Evaluation (CDE) in order to be able to start a clinical trial in China. After the trial, it can take another year or more for SFDA/CDE to approve the registration of the drug.

In principle, a fast track regulatory approval channel exists for certain new drugs, including those that demonstrate clinical effectiveness for rare diseases. However, in practice, the approval time for orphan drugs is not reduced, mainly due to staff shortages. As a result, the approval process for orphan drugs can take as long as non-orphan drugs.

Lack of financial incentives

Some countries provide financial incentives to encourage manufacturers to develop orphan drugs. In Japan, for example, the government covers up to 50% of the development costs for orphan drugs, grants a 6% tax reduction for research and development, and allows additional price premiums for orphan drugs. However, in China, there are no financial incentives or special pricing policies for orphan drugs.³

High rate of misdiagnosis

There is no special diagnostic or treatment center for orphan diseases in China. As for other serious diseases, patients are often diagnosed at local hospitals or community clinics, and then go to large hospitals for confirmation and treatment. Patients also have the option of going directly to large hospitals since no referral is required. Due to limited clinical expertise in orphan diseases, the rate of misdiagnosis is high. Overall, nearly half (48.3%) of patients with orphan diseases have been wrongly diagnosed.⁴ Therefore, even when orphan drugs are approved and available on the market in China, they may not reach the right patients.

Limited funding for high cost orphan drugs

High-cost orphan drugs are often excluded from reimbursement drug lists (RDLs), since price is a key driver for reimbursement decisions. As a result, the patients' out-of-pocket payment is significant, and the use of highcost orphan drugs is limited by patients' ability to pay. The sources of funding for orphan drugs are discussed below.

Future market access environment

While efforts are being made in China to better understand orphan diseases, the changes in the government legislation and policies will likely take a long time. In the next five years, there are no significant changes expected, and the market access environment for orphan drugs will likely remain challenging.

Funding sources for orphan drugs

Three main sources of funding exist for orphan drugs in China: (1) funding through government (at national, regional or local level), (2) funding through charity, and (3) funding by patients' out-of-pocket (OOP) payment. While these multiple funding channels exist, provincial/ local government funding and patients' out-of-pocket payments are currently the most important sources of funding for high-cost orphan drugs.

Funding through government

National reimbursement drug list (national RDL)

As for non-orphan drugs, it can take several years for orphan drugs to be included on the national RDL after market authorization by the SFDA, and the criteria for inclusion on the national RDL are broadly the same for both orphan and non-orphan drugs. Efficacy and price are the two key drivers for reimbursement decisions. As a result, high-cost orphan drugs are often excluded from the national RDL.

Drugs for orphan diseases that are reimbursed at 100% on the national RDL are often low-cost and generally produced by local manufacturers. Higher cost drugs are either partially reimbursed or not covered at all.

Provincial/local reimbursement drug list (provincial/local RDL)

Drugs that are not included on the national RDL can be reimbursed in some provinces or cities through inclusion on the provincial/local RDL. Healthcare budgets are managed at the provincial/local level; therefore, depending on the local needs and ability to

Disease Name	Drug Name	Reimbursement Level	Price (RMB)	Maker
Non-Hodgkin's lymphoma	Rituximab	Partial in some provinces	3,980 (100mg/10ml)	Roche
Neonatal respiratory distress syndrome	Poractant Alfa Injection	Partial in some provinces	8,084 (3ml; 0.24 g)	Chiesi Farmaceutici S.p.A.
Chronic myelogenous leukemia and gastrointestinal stromal tumors	Imatinib	Partial in some provinces	25,500 (100mgx120)	Novartis
Advanced non-small cell lung cancer	Gefitinib	Partial in Guang Zhou City	5,000 (0.25g×10)	AstraZeneca

Table 1: Examples of high-cost drugs for orphan diseases that are included on provincial/local RDLs, but not the national RDL

pay, some provinces or cities may include some highcost drugs in their RDL (which are not on the national RDL), or increase the level of reimbursement to 100% for the drugs that are only partially reimbursed on the national RDL (See Table 1). Consequently, provinces and cities are driving the reimbursement for high-cost orphan drugs.

Serious disease coverage

For diseases that are considered a high-cost burden on patients and families, serious disease coverage provides additional reimbursement, on top of basic medical insurance, to patients with limited financial resources. While the numbers of diseases covered under the serious disease coverage has expanded recently and includes certain orphan diseases such as hemophilia and chronic myeloid leukemia, the level of coverage is still quite low due to limited funding. For the serious disease coverage to be of relevance to high-cost orphan drugs funding, substantial cash injections will be needed.⁵

Funding through charity

Drug donation via charity

Some high-cost orphan drugs that are not reimbursed are provided by manufacturers free of charge to patients through charitable organizations. China Charity Federation (CCF) is one of the most influential charity organizations in China. High-cost orphan drugs donated by manufacturers through CCF include Cerezyme by Genzyme for Gaucher's disease, Gleevec by Novartis for chronic myeloid leukemia, and Exjade by Novartis for beta-thalassemia.

Charity donations by manufacturers can help in raising awareness of the orphan disease and the drug of interest among key stakeholders, which could lead to reimbursement in the future, as seen in this Cerezyme case study:

Over 10 years ago, Genzyme began donating Cerezyme free of charge to patients with severe Gaucher's disease in China, first through the World Health Foundation, and then through the CCF beginning in 2008. As well as donating drugs for free, the manufacturer worked closely with the CCF to increase public awareness of the disease and promote research into policy and insurance coverage for orphan diseases. Possibly as a result of these efforts, Cerezyme has recently been reimbursed in the city of Qingdao.

Fundraising via charity

Public fundraising through charitable organizations provides another route of funding for orphan drugs, as seen with the recent success of the ice bucket challenge for Amyotrophic Lateral Sclerosis (ALS), which was introduced in China in August 2014 and spread rapidly.⁸ As the people in China have more disposable income and have become more involved in charitable activities, public fundraising could represent an increasingly important source of funding for high-cost orphan drugs. Currently, the fundraising right is restricted to only a few charities, which are often large and linked to the government. For public fundraising to have a greater impact on orphan drug funding, the current restrictions on fundraising rights need to be addressed to allow more charitable organizations to be able to fundraise.

Out-of-pocket payment by patients

Because of limited funding currently available, patients' out-of-pocket payments for orphan drugs is significant. Overall, almost 80% of patients with orphan diseases have less than 10% of their total treatment costs reimbursed, and only approximately 10% of patients have more than 50% of the total treatment cost reimbursed. High OOP payments impose a significant burden for the patient and family, with more than 70% of families expressing concern for their ability to afford their treatment.⁴

Qingdao City as an example

The city of Qingdao has been leading the way for orphan drug funding in China, with the local government actively providing coverage for orphan diseases. In 2012, the local government issued a policy to cover two orphan diseases together with other major diseases, and provided direct funding for these diseases. In 2014, the coverage was expanded to include six additional orphan diseases, with several high-cost orphan drugs reimbursed (See Table 2). The orphan diseases covered in Qingdao include hemophilia, tetrahydrobiopterin deficiency (BH4 deficiency), Gaucher's disease and acromegaly.

With the funding from the Qingdao local government and charitable donations, the treatment cost to patients with orphan diseases can be as low as 10 to 15%.⁷

While the drivers for the Qingdao government's progressive stance toward orphan diseases funding are uncertain, it is clear that its local government considers funding for major diseases and orphan diseases to be a public health priority. The ability of Qingdao to fund high-cost orphan drugs is also helped by its strong financial resources. For manufacturers with high-cost orphan drugs, the city of Qingdao could represent a gateway to market access in China.

Future funding sources for orphan drugs

In the next five years, provinces/cities will likely continue to drive the reimbursement for high-cost orphan drugs, and charity will become increasingly important for providing funding for them and also for raising awareness. As a result, patients' out-of-pocket payment levels could be reduced, but overall will still remain significantly high in the short term. Table 2: Examples of orphan diseases and high-cost orphan drugs that are covered by the Qingdao government

Disease Name	Drug Name	Price (RMB)	Maker
Hemophilia	BeneFIX (recombinant human coagulation factor IV)	6800 (1000IU)	Pfizer
Tetrahydrobiopterin deficiency (BH4 deficiency)	Kuvan (saprotein dihydrochloride tablets)	Not available	Merck
Multiple sclerosis	Betaferon, recombinant human interferon beta – 1b	13,000 (800IU)	Schering
Primary pulmonary hypertension	Bosentan tablets	31,630 (125mg*56)	Actelion
Acromegaly	Somatuline	4,260 (40mg)	lpsen
Gaucher's disease	Cerezyme (imiglucerase)	29,741 (400 units/bottle)	Genzyme

Key stakeholders for market access of orphan drugs

Currently, the most important stakeholders for highcost orphan drug funding are regional policy makers and regional pricing and reimbursement bodies. National level pricing and reimbursement bodies are less important in terms of access of high-cost orphan drugs. Charity also plays an important role in funding, raising awareness and potentially providing a bridge to reimbursement in the long term (as was the case for Cerezyme). Other organizations, such as patient advocacy groups, medical organizations and manufacturer organizations have limited influence.

In the next five years, provincial/regional stakeholders will remain important for funding high-cost orphan drugs. Charity will likely become increasingly important for providing funding and raising awareness.

Implications, action plans and key consideratons for manufacturers Implications

As mentioned earlier, multiple challenges exist (and are expected to remain in place for the next five years) for the market access of orphan drugs in China, all of which can impact the bottom line for manufacturers.

• The lack of legislation and incentives means there is a lack of public health recognition among key stakeholders for orphan drugs, which could negatively impact priorities among policy makers and budget allocation for orphan drugs at the national, regional, and local levels.

- The slow market authorization for drugs, including orphan drugs, means there will be a delay in revenue generation and return on investment.
- The price control of reimbursed drugs means that there is pressure on the manufacturers to reduce price in order for high-cost orphan drugs to be reimbursed.
- The limited reimbursement for orphan drugs means that there is a high-cost burden on patients and their families, and the market uptake will be limited by the patients' ability to afford the drugs.
- The high rate of misdiagnoses means that even when orphan drugs do reach the market, it is difficult for them to reach the right patients and for meaningful real-world evidence to be gathered.

Action plans

Short term: Work with charitable organizations

Many of the challenges in the market access of orphan drugs in China are driven by the lack of awareness and subsequent lack of priority among the key stakeholders for orphan diseases. Charity provides a valuable pathway for fundraising, as well as building relationships with and influencing key stakeholders, since most of the large charitable organizations are linked to the government.

Medium term: Seek reimbursement at the provincial and local levels

The goal for manufacturers in a medium term is to seek reimbursement at provincial/local levels. This will require continued effort in order to support funding allocation and reimbursement decisions, including working with senior sponsors in government, key opinion leaders, and charities, as well as educating and influencing key stakeholders on the importance of orphan disease funding and the value of the orphan drugs of interest.

Long term: Continue efforts to drive policy changes leading to a more favorable environment

For long-term change, manufacturers need to continuously work with charities, senior sponsors, and key opinion leaders to influence policy makers in order to support changes in legislation and policy and promote a more favorable market access environment for orphan drugs in China.

Considerations

Should an orphan drug be launched at all, given the challenges?

The current environment is not likely to change in the short term. Delaying launch could lead to missed opportunities, particularly in out-of-pocket payments. Whether to launch an orphan drug in China or not would depend on a number of factors, including 1) the level of the unmet need in the orphan disease of interest in China, 2) how well the drug addresses the unmet need, 3) the size of the eligible patient population in China, and, 4) the size of the out-of-pocket payment market if the drug is not reimbursed on the RDL.

When should an orphan drug be launched? Should it wait until the market environment is more favorable? Given that the market access environment is not likely to change in the short term, having the drug on the market early will help manufacturers start raising awareness for the orphan drug of interest early and increase market presence of the product. It will also help gain physician confidence in using the product and support from key opinion leaders, who can then influence budget holders. Furthermore, for a drug to be reimbursed, it has to be on the market in China for a certain period of time, typically two years or more.

What is the best way to prepare for the launch?

Work with key opinion leaders to educate payers as early as possible on the severity of the disease, the value of the orphan drug of interest, and the importance of funding. Manufacturers can also work with the relevant charities to raise funding, increase public awareness, and indirectly influence payers in order to support reimbursement in the long term.

What can be done once the product is on the market?

To optimize market uptake, continue to work with local and regional payers, charities, and key opinion leaders to support reimbursement. Work with physicians to gain support, as they play a key role in treatment choice. Working with patient organizations to increase patient awareness of the product is also valuable. This is particularly important if the drug is not reimbursed, in which case the patients themselves are the payers.

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- ⁴ Ying L. Policy Recommendations Regarding Rare Diseases in China an Analysis Based on a Survey of Living Conditions of the People with Rare Disease. *China Soft Sci Mag.* 2014; 2:77-89.
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- ⁷ QD. (2014). *Qingdao News Daily*. Accessed at: <u>http://www.dailyqd.com/2014-09/10/content_124889_all.htm</u>.
- ⁸ BJ. (2014). Beijing News. Accessed at: <u>http://epaper.bjnews.com.cn/html/2014-08/23/content_530720.htm</u>.

Upcoming Presentations



24th European Stroke Conference

May 13-15, 2015; Vienna, Austria

ORAL PRESENTATION

Estimating the Impact of Non-Vitamin K Oral Anticoagulants, Warfarin, and Aspirin on Outcomes among Non-Valvular Atrial Fibrillation Patients in Real-World Clinical Practice: A Systematic Review

Koufopoulou M, Zhang J, Ashaye AO, Jenkins A, Gosden T

AGS American Geriatrics Society Meeting

May 15-17, 2015; National Harbor, MD, USA

POSTERS

Heatlh Outcomes and Functional Status of Overactive Bladder among the Medically Complex Vulnerable Elderly in the United States

Chuang CC, **Yang E,** Zou KH, Araiza A, **Wang A**, Luo X

Healthcare Resource Utilization and Cost of Overactive Bladder among the Medically Complex Vulnerable Elderly in the United States

Chuang CC, **Yang E,** Zou KH, Araiza A, **Wang A**, Luo X

ATS American Thoracic Society International Conference

May 15-20, 2015; Denver, CO, USA

POSTERS

A New Approach for Identifying Patients with Undiagnosed, Clinically Significant COPD in Primary Care

Martinez FJ, Mannino DM, **Leidy NK**, Bacci E, Barr RG, Bowler RP, Han MK, Houfek JF, Make BJ, **Malley KG**, Meldrum CA, Rennard SI, Thomashow B, Walsh JW, Yawn B Aclidinium Bromide Improves COPD Symptoms Assessed Using the EXAcerbations of Chronic Pulmonary Disease Tool-Respiratory Symptoms Questionnaire: Pooled Analysis of Two Phase III Studies

Jones PW, **Leidy NK, Hareendran A,** Lamarca R, Chuecos F, Garcia Gil E

Using Multi-Criteria Decision Analysis (MCDA) to Understand Patient Preferences for COPD Treatment

Wilcox TK, Marsh K, Zaiser E, Orfanos P, Salverda S, Sun SX, Dixit S

Digestive Disease Week

May 16-19, 2015 Washington, DC, USA

POSTERS

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

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

APA Annual Meeting

May 16-20, 2015; Toronto, Canada

POSTERS

Health Resource Utilization and Costs for Schizophrenia Patients with Prior Atypical Antipsychotic Use Before and After Asenapine Initiation

Chitnis A, Sun SX, Dixit S, **Wang R, Tawah A**, Boulanger L

Healthcare Resource Use and Expenditures for Bipolar Disorder Patients on Asenapine with Prior Atypical Antipsychotic Use

Wang R, Chitnis A, Sun SX, Dixit S, Tawah A, Boulanger L

ASCO Annual Meeting

May 29-June 2, 2015; Chicago, IL, USA

POSTER

Patient-reported Outcome Instruments Meaningful and Relevant for Tenosynovial Giant Cell Tumor (TGCT): A Qualitative Study

Gelhorn H, Lenderking W, Murray L

McGill University, Summer Course

June 1-4, 2015; Montreal, Canada

COURSE

EPIB 654 PE IV: Pharmacoeconomics

J. Jaime Caro, MDCM, FRCPC, FACP, Chief Scientist, Evidera, and Adjunct Prof. of Medicine, and of Epidemiology and Biostatistics, McGill Univ., Montreal, Canada

COPD9 USA Congress

June 5-6, 2015; Chicago, IL, USA

POSTER

A New Method for Identifying Primary Care Patients Needing Spirometric Evaluation for COPD

Martinez F, Mannino D, **Leidy NK, Bacci ED**, Barr RG, Bowler RP, Han MK, Houfek JF, Make B, **Malley K**, Meldrum CA, Rennard S, Thomashow B, Walsh J, Yawn BP, for the High-Risk COPD Screening Study Group

WCD World Congress of Dermatology

June 8-13, 2015; Vancouver, Canada

ORAL PRESENTATION

Self-reported Facial Characteristics Associated with Aging and Facial Line Psychosocial Impact in a Diverse Sample of Men and Women from a Multinational Study

Goodman G, **Kawata AK,** Bessonova L, Gallagher CJ

EULAR Rome 2015

June 10-13, 2015; Rome, Italy

POSTER

Comparative Analysis of the Effectiveness of Anti-TNF Therapies in Non-radiographic Axial Spondyloarthritis Using Novel Statistical Techniques

Benedict A, Ishak KJ, Gal P, Proskorovsky I,

Cappelleri JC, Everiss T, Jones H, Hughes R, Jenkins A

MDS 19th International Congress of Parkinson's Disease and Movement Disorders

June 14-18, 2015; San Diego, CA, USA

POSTER

Implementing a Delphi Panel to Improve Understanding of Patient Characteristics of Advanced Parkinson's Disease

Antonini A, Odin P, **Kleinman L, Skalicky A,** Marshall T, Sail K, Onuk K

AAIC Alzheimer's Association International Conference

July 18-23, 2015; Washington, DC, USA

ORAL PRESENTATION

Assessment of the Incremental Prognostic Utility of Clinical Diagnosis in Equations for Disease Progression in Alzheimer's Disease

Ishak KJ, Kansal AR, Krotneva S, Tarko L

ISOQOL 22nd Annual Conference

Oct 21-24, 2015; Vancouver, BC, Canada

WORKSHOP

An Introduction to Health-Related Quality of Life Assessment

Heather Gelhorn, PhD, Sr. Research Scientist, Outcomes Research, Evidera; Kathleen W. Wyrwich, PhD, Exec. Dir., Ctr. of Excellence Outcomes Research, Sr. Research Leader, Evidera

INFORMS Healthcare 2015

July 29-31, 2015; Nashville, TN, USA

ORAL PRESENTATION

Investigating Steroid Withdrawal Strategies for Patients with Kidney Transplantations

Ferrand YB, Desai V, Kelton CML, Cavanaugh TM, Caro JJ, Goebel JW, Heaton PC

ASPMN 25th National Conference

September 16-19, 2015; Atlanta, GA, USA

POSTER

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

Datto C, LoCasale R, Wilson H, Coyne K

Recent Presentations

MAD-ID 18th Annual Meeting

May 7-9, 2015; Orlando, FL, USA

POSTER

Patterns of Initial Antimicrobial Therapy among Patients in US Hospitals with Serious Infections due to Carbapenem-Resistant Enterobacteriaceae (CRE)

Berger A, Bhurke S, Wang R, Zhao Q, Bhagnani T, Lodise TP

QCOR 2015

April 29-May 1, 2015; Baltimore, MD, USA

POSTERS

Health Outcomes Associated with Triple Antiplatelet Therapy for the Secondary Prevention of Atherothrombotic Event

Ozer-Stillman I, Whalen JD, Du M, Oguz M, Davies GM, Bash LD, Singhal P Healthcare Costs Following Stroke and Major Bleeding Events in Nonvalvular Atrial Fibrillation Patients

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

Impact of Short-term Anticoagulant Use on the Risk of Recurrent Venous Thromboembolism: Evidence from Insurance Claims in the United States

Merli G, Li Q, Kumar Raut M, Damaraju CV, Chitnis A, Chen S, Schein J, Bookhart B

AMCP Annual Meeting & Expo April 7-10, 2015;

San Diego, CA, USA

POSTERS

Characterizing Healthcare Resource Utilization and Costs Following Patterns of Immediate Release Hydrocodone Use

Wild H, **Kansal A, Chitnis A,** Bell JA, Holly P, Boulanger L, Ben-Joseph R

Extended Release Opioid Treatment Patterns Following Initiation of Immediate Release Hydrocodone

Burgoyne D, Brixner D, **Kansal A, Paramore C, Chitnis A,** Bell JA, Holly P, Ben-Joseph R

AAD American Academy of Dermatology Annual Meeting

March 20-24, 2015; San Francisco, CA, USA

ORAL PRESENTATION

Self-reported Facial Characteristics Associated with Aging in a Diverse Sample of Men and Women from a Multinational Web-based Panel Survey

Goodman G, **Kawata AK,** Bessonova L, Gallagher CJ

16th World Congress on Human Reproduction

March 18-21, 2015; Berlin, Germany

ORAL PRESENTATION

Cost of Unintended Pregnancy in Sweden: The Role of Increased Use of Long-acting Reversible Contraceptive Methods

Lovkvist L, Engstrand S, Filonenko A, Henry N, Kopp Kallner H, **Lambrelli D**

ACC 64th Annual Scientific Session

March 14-16, 2015; San Diego, CA, USA

POSTERS

Estimating the Lifetime Clinical Benefits of Apixaban versus Aspirin in the Low Risk Non-Valvular Atrial Fibrillation Patients in the US: How May Results from AVERROES Help Improve Patient Care?

Lip GYH, **Lanitis T,** Mardekian J, **Kongnakorn T,** Phatak H, Dorian P

Validation of the Apixaban Cost-Effectiveness Model in Patients with Venous Thromboembolism

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

NCCN 20th Annual Conference

March 12-14, 2015; Hollywood, FL, USA

POSTER

Cost and Health Outcomes of Continuation Rules for Second-line BCR-ABL Tyrosine Kinase Inhibitor (TKI) Use for Patients with Chronic Myelogenous Leukemia (CML)

Whalen J, Ozer-Stillman I, Ambavane A, Felber E, Bolinder B

THETA - Toronto Health Economics and Technology Assessment Collaborative Seminar Series

March 6, 2015; Toronto, Canada

ORAL PRESENTATION

Rolling the DICE: Can We Do Better Than Markov, DES, and Microsimulation?

Caro JJ

ENDO 2015

March 5-8, 2015; San Diego, CA, USA

POSTERS

Economic Burden of Obesity-related Comorbidities in an Electronic Health Records System in the United States

Huang JC, Li Q, Hammer M, Blume SW, Hobbs TM

Obesity-related Comorbidities Are Independent Drivers of High Healthcare Costs in the United States

Huang JC, Li Q, Blume SW, Hammer M

ISCTM 11th Annual Scientific Meeting

Feb 17-19, 2015; Washington, DC, USA

POSTER

Assessment of Improvement in Quality of Life with Bipolar Disorder: A Comparison of Analytic Approaches

Rajagopalan K, Ng-Mak D, **Dansie E, Wyrwich K,** Pikalov A, Loebel A

Tufts Medical Center's Cancer Center Grand Rounds Series

Feb 6, 2015; Boston, MA, USA

ORAL PRESENTATION

What is Health Technology Assessment? And, Why Should I Care?

Caro JJ

Banco Interamericano de Desarrollo (Inter-American Development Bank) Sponsored Webinar

Jan 29, 2015; Boston, MA, USA

ORAL PRESENTATION El Uso del Analisis Multicriterio de Decisiones en la Evaluacion de Tecnologias en Salud

Caro JJ

MauiDerm 2015 Meeting

Jan 26-30, 2015; Maui, HI, USA

POSTER

Self-reported Facial Characteristics Associated with Aging and Self-perception of Age Among a Diverse Sample of Aesthetically Naive Men and Women from a Multinational Study

Goodman G, Lambros V, **Kawata AK**, Bessonova L, Gallagher CJ

TOXINS 2015

Jan 14-17, 2015; Lisbon, Portugal

POSTER

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

Dinet J, Lambrelli D, Balcaitiene J



Evidera Presents at ISPOR's 20th Annual International Meeting

MAY 16-20, 2015 - PHILADELPHIA, PA, USA



SHORT COURSES

Sun., May 17, 8:00 AM - 12:00 PM Discrete Event Simulation for Economic Analyses – Concepts

J. Jaime Caro, MDCM, FRCPC, FACP, Chief Scientist, Evidera; Jorgen Moller, MSc Mech Eng, VP Modeling Technologies, Evidera

Sun., May 17, 1:00 - 5:00 PM Discrete Event Simulation for Economic Analyses – Applications

J. Jaime Caro, MDCM, FRCPC, FACP, Chief Scientist, Evidera; Jorgen Moller, MSc Mech Eng, VP Modeling Technologies, Evidera

Sun., May 17, 1:00 - 5:00 PM Using Multi-Criteria Decision Analysis in Health Care Decision Making: Approaches & Applications

Maarten IJzerman, PhD, Prof. & Head, Univ. of Twente; **Kevin Marsh**, PhD, Sr. Research Scientist and Dir., Modeling & Simulation, Evidera; Nancy Devlin, PhD, Dir. of Research, Office of Health Economics; Praveen Thokala, PhD, MASc, Research Fellow, ScHARR, Univ. of Sheffield

WORKSHOPS

Session III – Tues., May 19, 5:00 - 6:00 PM W15: The ISPOR MCDA Task Force: How Best to Use it in Health Care Decision Making

Maarten IJzerman, PhD, Prof. & Head, Univ. of Twente; Nancy Devlin, PhD, Dir. of Research, Office of Health Economics; Praveen Thokala, PhD, MASc, Research Fellow, ScHARR, Univ. of Sheffield; **Kevin Marsh**, PhD, Sr. Research Scientist and Dir., Modeling & Simulation, Evidera

W19: Modeling in Oncology: The Taming of the Shrews?

Noemi Muszbek, MSc, Sr. Research Scientist, Evidera; Sorrel Wolowacz, PhD, Head European Health Economics, RTI Health Solutions; Agnes Benedict, MSc, Exec. Dir., Center of Excellence Health Economics and Sr. Research Scientist, Evidera **W21:** Statistical Methods Used for the Assessment of Non-Redundancy among Clinical Trial Endpoints

Elizabeth D. Bacci, PhD, Sr. Research Associate, Outcomes Research, Evidera; Randall H. Bender, PhD, Sr. Psychometric Statistician, Outcomes Research, Evidera; Joseph C. Cappelleri, PhD, Sr. Dir. Pfizer; Kathleen W. Wyrwich, PhD, Exec. Dir., Center of Excellence Outcomes Research and Sr. Research Leader, Outcomes Research, Evidera

RESEARCH PODIUM PRESENTATIONS

Session I – Mon., May 18, 2:15 - 3:15 PM

MO2: A Comparison of State Transition and Discrete Event Modeling Approaches for Antiplatelet Use in the Secondary Prevention of Thrombotic Events after Myocardial Infarction (MI)

Ozer-Stillman I, Whalen JD, Bash LD, **Du M,** Oguz M, Singhal PK, Davies GM

Session II – Mon., May 18, 3:45 - 4:45 PM

HE2: Explaining the Excess Home Healthcare Use and Expenditures among Elderly Medicare Beneficiaries with Parkinson's Disease

Bhattacharjee S, Metzger A, Tworek C, Wei W, **Pan X,** Sambamoorthi U

POSTERS

Session I – Mon., May 18, 8:30 AM - 2:15 PM **PRM143:** Important Statistical Considerations for Developing Equations for Disease Simulators

Ishak KJ, Kansal A, Krotneva M, Tarko L, Tafazzoli A

PDB81: Patient Reported Outcome Profiles of Adults Receiving Medical Care at Specialty Clinics for Chronic Pain and Diabetes

Amtmann D, Patel KV, **Bacci ED,** Bamer AM, Turk DC **PDB63:** Prevalence and Treatment of Genitourinary Conditions among Patients with Type 2 Diabetes Mellitus

Gries K, Cai B, Yu R, Kuti E, Sander S, Hareendran A

PRM93: What Type of Response Scale is the Most Responsive? A Comprehensive Review of Response Scale Options for Patient-Reported Outcome Measures

Rudell K, **Vernon MK, Gries K, Safikhani S,** DeLozier A, McQuarrie K, Norquist J, Coons SJ

Session II – Mon., May 18, 3:45 - 7:45 PM

PMH31: Changes in Healthcare Costs Associated with the Treatment of Bipolar Disorder Following Initiation of Asenapine versus Aripiprazole

Chitnis A, Wang R, Sun SX, Dixit S, **Tawah A,** Boulanger L

PMH66: Health Resource Use of Patients Enrolled to Janssen Connect and Treated with Long-acting Injectable (LAI) Atypical Antipsychotics: Preliminary Results from a Summative Evaluation

Benson C, Boulanger L, **YangE, Pan X, Payne K,** Fastenau J

PMH29: Healthcare Resource Utilization and Costs for Schizophrenia Patients Initiating Asenapine or Another Branded-Atypical Antipsychotic Medication

Nguyen K, **Chitnis A**, Sun SX, Dixit S, **Wang R**, **Tawah A**, Boulanger L

PIH51: Impact of Symptomatic Burden among Women Diagnosed with Uterine Fibroids on Health-Related Quality of Life: An Assessment Using Uterine Fibroid Symptom and Quality of Life Questionnaire (UFS-QOL)

Soliman AM, **Margolis MK**, Castelli-Haley J, **Coyne KS**

PMH46: Qualitative Study of Patients' Preferences for Bipolar Depression Treatment

Ng-Mak D, **Poon JL**, Rajagopalan K, **Kleinman L, Roberts L, Revicki D,** Loebel A Session III – Tues., May 19, 8:30 AM - 2:15 PM **PMS71:** Content Validity Evaluation of a New Diary Developed to Evaluate Symptoms Important to Patients with Moderate to Severe Rheumatoid Arthritis

DeLozier AM, Gaich CL, Vernon MK, von Maltzahn R

PRS27: Cost-Effectiveness Analysis of Smoking Cessation Interventions in Japan Using the Discrete Event Simulation Model

lgarashi A, Goto R, Yoshikawa R, Suwa K, **Ward AJ, Moller J**

PCV9: Estimating the Lifetime Clinical Risk/Benefits of Apixaban versus Edoxaban in Non-Valvular Atrial Fibrillation

Phatak H, Dorian P, **Kongnakorn T, Lanitis T,** Liu X, Mardekian J, Lawrence J, Lip G

PRS6: Impact of Change in Lung Function and COPD-Related Patient Outcomes on Exacerbations and Hospitalizations: A Systematic Literature Review

Donohue JF, Marvel J, Martin AL, Travers KU, Cadarette S, Wilcox TK

PSS28: Measurement Properties of the Patient-Reported Psoriasis Symptom Inventory Daily Diary in Patients with Moderate to Severe Plaque Psoriasis

Viswanathan HN, Mutebi A, Milmont CE, Gordon K, **Wilson H,** Zhang H, Klekotka P, **Revicki D,** Augustin M, Kricorian G, Nirula A, Strober B

PMS69: Patient-Reported Physical Function Outcome Measure for Adults with Fibrodysplasia Ossificans Progressiva: Intelligent Test Design Based on PROMIS Item Banks

Mattera MS, Kaplan FS, Pignolo RJ, Grogan D, Revicki D

PRS8: Real-World Observational Study of Association between Statin Medications and COPD-Specific Outcomes

Ajmera MR, Sambamoorthi U, Rust G, **Pan X,** Tworek C, Metzger A **PSS30:** Sensitivity of Functional Reading Independence (FRI) Index to Change in Size of Geographic Atrophy

Kapre AW, **Kimel M**, Bressler N, Varma R, Souied EH, Dolan C, Tschosik E, **Leidy N**

PCV54: Treatment Effects on the Cost Burden of Hospitalizations in Patients with Chronic Systolic Heart Failure

Kansal A, Kielhorn A, Dorman E, Krotneva S, Zheng Y, Patel H, Borer J

Session IV – Tues. May 19, 3:45 AM - 7:45 PM **PCN110:** Mapping Utility Scores from European Organization for Treatment of Cancer Core-30 Questionnaire Scores (EORTC QLQ-C30) in Relapsed Multiple Myeloma

Ashaye AO, Zhang J, Bender RH, Altincatal A, Panjabi S

PIN94: Projecting Changes in Total Days of Therapy (DOT) in Patients Hospitalized for Acute Bacterial Skin and Skin Structure Infection (ABSSSI)

Berger A, Kauf T, Oster G

Session V – Wed., May 20, 8:30 AM -2:45 PM PHS30: Assessing the Full Burden of Care for Agitation in Patients with Schizophrenia and Bipolar I Disorder

Margolis MK, Bapat B, Blume S, Cicero S, Gandhi SK

PSY36: Demonstrating the Cost Effectiveness of Movantik for the Treatment of Opioid Induced Constipation in Patients with Inadequate Response to Laxatives: A UK Perspective

Lawson R, Vioix H, Mudunkotuwe S, King F, Goh J, Marsh K

PHS29: Differences in the Total Healthcare Costs During the Year of Diagnosis between Appalachian and a National Cohort of Elderly Women with Breast Cancer: An Application of Decomposition Technique

Vyas A, Madhavan SS, Sambamoorthi U, **Pan X,** Regier M, Hazard H

PSY30: Direct Healthcare Costs of Opioid Abuse in Patients Prescribed Immediate Release Hydrocodone in the United States

Michna E, **Chitnis A, Paramore C,** Holly P, Bell JA, BenJoseph R

PND72: Parkinson's Disease and Caregiver Burden: Results from the National Alliance of Caregiving Survey

Bhattacharjee S, Metzger A, Tworek C, Wei W, **Pan X,** Sambamoorthi U



Publications

Abogunrin S, Di Tanna GL, Keeping S, Carroll S, Iheanacho I. Prevalence of Human Papillomavirus in Head and Neck Cancers in European Populations: a Meta-analysis. *BMC Cancer*. 2014 Dec 17; 14(1):968.

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 Nov; 17(11):771-81. Epub 2014 Aug 26.

Baldwin HE, **Kawata AK**, Daniels SR, **Wilcox TK**, Burk CT, Tanghetti EA. Impact of Female Acne on Patterns of Health Care Resource Utilization. *J Drugs Dermatol*. 2015 Feb 1; 14(2):140-148.

Bloor A, De Cock E, Hatswell AJ, **Wasiak R**, Elvidge J, Stapelkamp C, Hadjivassileva T, Haiderali A, Delgado J. Survival Outcomes and Treatment Costs for Patients with Doublerefractory Chronic Lymphocytic Leukaemia (DR-CLL). *Br J Haematol*. 2014 Nov 20 [Epub ahead of print].

Blume SW, Li Q, Huang JC, Hammer M, Graf TR. Variation in the Risk of Progression between Glycemic Stages across Different Levels of Body Mass Index: Evidence from a United States Electronic Health Records System. *Curr Med Res Opin.* 2015 Jan; 31(1):115-24. Epub 2014 Oct 16.

Bow EJ, Vanness DJ, Slavin M, Cordonnier C, Cornely OA, Marks DI, Pagliuca A, Solano C, **Cragin L**, Shaul AJ, **Sorensen S**, Chambers R, Kantecki M, Weinstein D, Schlamm H. Systematic Review and Mixed Treatment Comparison Meta-analysis of Randomized Clinical Trials of Primary Oral Antifungal Prophylaxis in Allogeneic Hematopoietic Cell Transplant Recipients. *BMC Infect Dis.* 2015 Mar 17;15(1):128.

Capkun G, Lahoz R, Verdun E, Song X, Chen W, Korn JR, Dahlke F, Freitas R, **Fraeman K**, **Simeone J**, Johnson BH, **Nordstrom B**. Expanding the Use of Administrative Claims Databases in Conducting Clinical Real-world Evidence Studies in Multiple Sclerosis. *Curr Med Res Opin*. 2015 Feb 7:1-37 [Epub ahead of print].

Cardozo L, Staskin D, **Currie B, Wiklund I**, Globe D, Signori M, Dmochowski R, MacDiarmid S, Nitti VW, Noblett K. Validation of a Bladder Symptom Screening Tool in Women with Incontinence Due to Overactive Bladder. *Int Urogynecol J*. 2014 Dec; 25(12):1655-63. Epub 2014 May 24.

Caro JJ. Psst, Have I got a Model for You ... Med Decis Making. 2015 Feb; 35(2):139-41. Epub 2014 Nov 20. Caro JJ, Moller J. Decision-Analytic Models: Current Methodological Challenges. Pharmacoeconomics. 2014 Oct; 32(10):943-950. Epub 2014 Jul.

Casper C, **Teltsch DY**, Robinson D Jr, Desrosiers MP, **Rotella P**, Dispenzieri A, Qi M, Habermann T, **Reynolds MW.** Clinical Characteristics and Healthcare Utilization of Patients with Multicentric Castleman Disease. *Br J Haematol.* 2015 Jan; 168(1):82-93. Epub 2014 Sep 11.

Chitnis AS, Ganz ML, Benjamin N, Langer J, Hammer M. Clinical Effectiveness of Liraglutide Across Body Mass Index in Patients with Type 2 Diabetes in the United States: A Retrospective Cohort Study. Adv Ther. 2014 Sep; 31(9):986-99. Epub 2014 Sep 23.

Chuang CC, **Bhurke S**, Chen SY, Brulais S, Gabriel S. Clinical Characteristics, Treatment Patterns and Economic Burden in Patients Treated for Neuroendocrine Tumors in the United States: a Retrospective Cohort Study. *J Med Econ*. 2015 Feb; 18(2):126-36. Epub 2014 Nov 5.

Ciarametaro M, Bradshaw SE, Guiglotto J, Hahn B, Meier G. Hidden Efficiencies: Making Completion of the Pediatric Vaccine Schedule More Efficient for Physicians. *Medicine* (*Baltimore*). 2015 Jan; 94(4):e357.

Coles V, **Chapman R, Lanitis T,** Carroll S. The Costs of Managing Genital Warts in the UK by Devolved Nation: England, Scotland, Wales and Northern Ireland. *Int J STD AIDS*. 2015 Feb 12 [Epub ahead of print].

Coons SJ, **Eremenco S**, Lundy JJ, ODonohoe P, OGorman H, Malizia W. Capturing Patient-Reported Outcome (PRO) Data Electronically: The Past, Present, and Promise of ePRO Measurement in Clinical Trials. *Patient*. 2014 Oct 10 [Epub ahead of print].

Coons SJ, **Eremenco S**, Lundy JJ, ODonohoe P, OGorman H, Malizia W. Erratum to: Capturing Patient-Reported Outcome (PRO) Data Electronically: The Past, Present, and Promise of ePRO Measurement in Clinical Trials. *Patient*. 2015 Feb 21 [Epub ahead of print].

Coyne K, Currie B, Thompson C, Smith T. The Test-Retest Reliability of the Peyronies Disease Questionnaire. J Sex Med. 2015 Feb; 12(2):543-8. Epub 2014 Nov 17.

Coyne KS, Currie BM, Holmes WC, Crawley JA. Assessment of a Stool Symptom Screener and Understanding the Opioid-induced Constipation Symptom Experience. *Patient*. 2014 Sep 18 [Epub ahead of print]. Coyne KS, Currie BM, Thompson CL, Smith TM. Responsiveness of the Peyronie's Disease Questionnaire (PDQ). J Sex Med. 2015 Feb 9 [Epub ahead of print].

Coyne KS, Margolis MK, Yeomans K, King FR, Chavoshi S, **Payne KA**, LoCasale RJ. Opioid-Induced Constipation Among Patients with Chronic Noncancer Pain in the United States, Canada, Germany, and the United Kingdom: Laxative Use, Response, and Symptom Burden Over Time. *Pain Med.* 2015 Mar 20 [Epub ahead of print].

Coyne KS, Sexton CC, Thompson C, Bavendam T, Brubaker L. Development and Psychometric Evaluation of the Urgency Questionnaire for Evaluating Severity and Health-related Quality of Life Impact of Urinary Urgency in Overactive Bladder. Int Urogynecol J. 2015 Mar; 26(3):373-82. Epub 2014 Jun 19.

Coyne KS, Thompson CL, Lai JS, Sexton CC. An Overactive Bladder Symptom and Healthrelated Quality of Life Short-form: Validation of the OAB-q SF. *Neurourol Urodyn.* 2015 Mar; 34(3):255-63. Epub 2014 Jan 13.

Craig BM, Reeve BB, Brown PM, Cella D, Hays RD, Lipscomb J, Simon Pickard A, **Revicki DA.** US Valuation of Health Outcomes Measured Using the PROMIS-29. Value Health. 2014 Dec; 17(8):846-53.

Delforge M, Minuk L, Eisenmann JC, Arnulf B, Canepa L, Fragasso A, Leyvraz S, Langer C, Ezaydi Y, Vogl DT, Giraldo-Castellano P, Yoon SS, Zarnitsky C, Escoffre Barbe M, Lemieux B, Song K, Bahlis NJ, **Guo S,** Silva Monzini M, Ervin-Haynes A, Houck V, Facon T. Health-related Quality of Life in Patients with Newly Diagnosed Multiple Myeloma in the FIRST Trial: Lenalidomide Plus Low-dose Dexamethasone versus Melphalan, Prednisone, Thalidomide. *Haematologica*. 2015 Mar 13 [Epub ahead of print].

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COMPANY NEWS

CONGRATULATIONS! EVIDERA ANNOUNCES SENIOR LEVEL PROMOTIONS

Elizabeth Dansie Bacci, PhD Research Scientist, Outcomes Research Based in Seattle, WA

Heather Gelhorn, PhD

Senior Research Scientist, Outcomes Research Based in Seattle, WA

Luis Hernandez, MSc

Research Scientist, Modeling & Simulation Based in Lexington, MA

Leslee Masten, BA

Principal Market Access Writer, Payer Communications Based in Lexington, MA

Peter Quon, MPH

Research Scientist, Modeling & Simulation Based in Bethesda, MD

Tom Rising, MSc, DPhil

Principal, Payer Strategy Based in Lexington, MA

Jason Simeone, PhD

Research Scientist, Retrospective Observational Studies Based in Lexington, MA

John Whalen, BS

Research Scientist, Modeling & Simulation Based in London, UK

Evidera Welcomes New Senior Staff



Krista A. Payne, MEd,

has joined the Evidence Strategy Solutions team and serves in multiple capacities for the team, including Senior Principal Consultant, Senior Research Scientist and Executive Director roles.

In these roles, she offers strategic leadership in the development

of value propositions for new products and helps to identify the appropriate methodologies that could be employed to generate the evidence required to achieve successful market access. She works with life science companies across all product phases to develop value demonstration strategies to meet multiple stakeholder needs and maximize market potential. Ms. Payne offers 20 years of experience in evidence development planning to meet post-approval requirements and market uptake for healthcare treatments, and real-world study design across a diversity of retrospective and prospective methodologies. Over the course of her career, Ms. Payne has successfully led departments responsible for the strategic development and planning, as well as the design and conduct, of studies used by pharmaceutical sponsors to demonstrate effectiveness, burden of illness, unmet need, resource utilization, medication adherence, and treatment satisfaction. Ms. Payne has managed several international health economic projects and has served as a principal investigator for numerous multinational observational studies and periand post-approval programs. In 2014, Ms. Payne was honored by PharmaVoice as one of the top 100 most inspiring pharma industry professionals for her scientific leadership and team building contributions to business success and client satisfaction. Ms. Payne has served as chairperson and presenter at various scientific meetings and industry forums, and she has published more than a dozen scientific manuscripts in peer-reviewed journals. Ms. Payne received her Bachelor's degree in Psychology from Queen's University in Kingston, Ontario, Canada, and her Master's degree in Educational Psychology from McGill University in Montreal, Quebec, Canada.



Baris Deniz, MS,

is a Senior Research Scientist with Evidera's Modeling & Simulation team in Bethesda, MD.

Mr. Deniz's responsibilities include the development of health economic models for submission to reimbursement agencies globally, supporting development of payer value

stories that are aligned with broader commercial and medical value propositions, and providing oversight for the strategic dissemination of the study findings. Mr. Deniz has 10+ years of experience in the market access and reimbursement area working on a wide variety of therapeutic areas and therapy classes. Prior to joining Evidera, Mr. Deniz served in various roles and capacities both within the industry and consultancy side of the business. While he specializes in decision analytic modeling and advanced model design, his unique background that combines extensive experience on leading market access launch initiatives, continued support of marketed products post-launch, and strategic alignment of market access activities with other key functions, such as commercial and medical teams, enables him to provide custom solutions fit for purpose via leveraging health economic and outcomes tools. Mr. Deniz's work has been presented at various national and international conferences and has been published in various respected journals. Mr. Deniz received his BS degree in Mechanical Engineering with a focus on numerical methods and modeling, and his MS degree in Operations Research with a focus on mathematical modeling, statistics, and simulation methodologies at Northeastern University.





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