ESTABLISHING HEALTH TECHNOLOGY ASSESSMENT IN RUSSIA

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Director, Center of Comprehensive Health Technology Assessment
Ministry of Health, Russian Federation
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Establishing Health Technology Assessment in Russia

An Interview with Vitaly Omelyanovskiy

Director, Center of Comprehensive Health Technology Assessment
Ministry of Health, Russian Federation

Vitaly Omelyanovskiy, MD, PhD, DSc, is a Professor of the Presidential Academy, awarded the Certificate of Merit of the Federal Assembly of the Russian Federation, an initiative of the Federation Council Committee on Social Policy for his many years of dedication, hard work, and contributions to the improvement of the legislation of the Russian Federation on the issues of public health and health economics. He is a Head of the HTA Research Center, Institute of the Applied Economic Research, a Chairman of the Expert Board of Healthcare of the Russian Council Committee on Social Policy, a Chairman of the Board of the National Center for Health Technology Assessment in Healthcare of the Russian Federation, and the President of the ISPOR Russia HTA Chapter.

You have been given the responsibility for the establishment of the Center for Comprehensive Health Technology Assessment (Center) at the Russian Federation’s Ministry of Public Healthcare. Congratulations on such an important and high profile position. I am sure this will have a great effect on market access in Russia.

Thank you. We have not yet finalized the establishment of the Center which I have led since May 2015. It was originally responsible for the certification of medicine, and we have been going through the process of evaluating the aim, goals, and responsibilities – as well as the name – to meet the changing needs of our healthcare system.

You said in a recent presentation that we will witness increasing transparency of health technology assessment (HTA) development in the years to come in Russia. I’m sure our readers will be pleased to hear this. Would you outline the motivation for this push for transparency?

This interview was conducted by Kevin Marsh, PhD, Senior Research Scientist and Senior Director, Modeling & Simulation, Evidera.
Discussions on HTA began in Russia in 2009 when the GDP was higher than it is now, and there was a significant investment in the healthcare system. Recently the economic situation has worsened, so we began working with relevant stakeholders, including medical societies, political officials, etc., to think about the need for HTA. There was an agreement that decisions about investments in medicines needed to be made in a more independent and transparent manner.

For the last three years, Russia has implemented a DRG [diagnosis-related group] system as a way of controlling hospital spending, so now we will have HTA and DRG approaches to control spending in our healthcare system and make the system more efficient and transparent.

Could you provide an overview of the process for implementing new HTA approaches in Russia and the timeframe over which this will happen?

Starting in 2014, our government implemented a system where a Minister of Health would invite experts from different federal organizations, such as universities and medical centers, to provide expertise on the inclusion of medicines on essential drug lists, reimbursement lists, etc.

Our work starts there. We have to coordinate this process and improve its transparency, including working with expert groups to assess their knowledge and use their expertise in the best ways; educating stakeholders in the use of HTA; and developing methodologies and decision-making criteria.

This process will begin in November 2015, and we need to do this before the next version of the Essential Drug List (EDL) is created, which will start in August 2016. My hope is that by then we will have an improved process based on different rules, skills and procedures. This gives us approximately six months to develop a new methodology and processes. Once the processes are established, we will communicate these requirements, guidelines, and methodologies to industry, expert organizations, and all key opinion leaders to ensure everyone’s expectations are aligned. In the end, we want to ensure appropriate assessments are being made on every level.

I appreciate that the Center is still a work in progress, but can you say anything about the likely scope of the Center? For instance, one of the novel features of the Russian system is a mix of federal, regional and other funding sources. Do you anticipate that system would remain the same? And if so, where does the Center fit in? Is the Center just intended to support federal decision making?

I see that both the federal and regional levels will still have a place in the system for at least the next five to ten years. Russia is a very big country and we have more than 80 regions with different systems and budgets. I believe we will have federal decisions, and the Minister of Health would like these to establish the minimum care that everyone would have the opportunity to receive, with individual regions being able to provide care on top of this minimum, but they would be obliged to at least meet this minimum.

In terms of the specific technologies that the Center will consider, is the role of the Center to be assessing all technologies that are applying for the Vital and Essential Drug List?

First of all, let me say that in accordance with our federal law, HTA is only to be used for the assessment of medicines. Views are changing, however, and it is the hope that in the coming years HTA will be applied not only to medicines, but to different technologies like medical devices. I also expect to see potential changes in clinical guidelines in accordance with the principles of HTA.

Yes. The Essential Drug List is a federal responsibility, and all spending from the federal budget should be assessed by our Center. First we will start with medicines, but I hope this will eventually include medical devices and other technologies as well.

Would there be any special provision made for special cases like oncology or orphan drugs? And do you anticipate assessments being done retrospectively or just prospectively for new technologies?

“The Essential Drug List is a federal responsibility, and all spending from the federal budget should be assessed by our Center.”

– Vitaly Omelyanovskiy
This is a difficult challenge and a controversial topic. I believe we will be involved in these assessments since federal spending would be involved. Many of these products are very expensive, so input will be needed on which products should be prescribed. However, making the process transparent, and creating and disseminating a methodology, will be challenging. We will look at different approaches, such as multi-criteria decision making (MCDA), to help overcome these challenges. There is a huge lobby from orphan drug companies and patient groups to make these treatments available, so there is a lot of work to be done to identify how to make these treatments available, negotiate with all key stakeholders, and create agreement among all parties.

You mentioned MCDA. Is that a method that you would like to see play a role in Russia?

I would say yes. From my point of view, it is a very useful and effective system to make assessments. Unfortunately, conventional HTA cannot cover all the different aspects of decision making, especially when thinking about efficacy, safety, and economic issues. We know that MCDA could be used not only in medicine, but also in many different areas where we need to make decisions about investment where there are many factors to consider.

When we speak about MCDA in the healthcare system, I see this being used in something like orphan drug evaluation. We have to think about safety, efficacy, and economics, but also about when the disease will start, when it will end, and all the quality of life issues associated with it. MCDA would allow us to think more widely and incorporate the interests of the many parts of the society to come to an agreed upon decision. It is my dream to use MCDA and we are in the process of achieving this. We are thinking about how to use MCDA to prioritize the diseases where we need to provide treatment at a federal level. This methodology would help us in creating a transparent process and in pushing officials to think in this direction.

Do you anticipate that the assessments that the Center undertakes will be made public so that they are transparent?

The process of making these decisions, seeing who participated and what the arguments were on both sides, will be available on the Internet and visible to the public. Just over the last two weeks, there was a negotiation process about the revision of the EDL. My agency was not included because we officially start in 2016, but we contributed to the reporting of the decision. So the first achievement is visibility and transparency. Second is the criteria for decision making. There is still plenty of work to be done to optimize the process, and that is where our Center will begin.

Is there anything else you would like to share with our readers about the changes occurring in Russia’s healthcare system and health technology assessment process?

There is a great deal of interest in this topic in Russia right now, and I am encouraged by the emphasis being put on the efforts to improve our overall processes. I realize that as head of the Center of Comprehensive Health Technology Assessment in Russia there is a great deal of work ahead of us and it will not be easy. Moreover, I fully expect there will be challenges along the way and it will take time to make these system changes, but I am also looking forward to the possibilities that lie ahead for us. The creation of my agency is movement in a positive direction to bring better processes, guidelines, transparency, and education to our healthcare decision making.
FDA Qualification of Plasma Fibrinogen as a Biomarker for Clinical Trials of Chronic Obstructive Pulmonary Disease

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Research Scientist, Real-World Evidence, Evidera

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Clinical Development Director, GlaxoSmithKline

Introduction

In 2004, the U.S. Food and Drug Administration (FDA) published a report titled “Innovation or Stagnation: Challenge and Opportunity on the Critical Path to Medical Products,” which concluded that significant improvements should be made to the drug development process. The creation of drug development tools (methods, materials, or measures, including biomarkers) is an important component of that process. The FDA’s Biomarker Qualification Program was designed to support the development of biomarkers as a drug development tool, and a guidance document was issued to support external stakeholders in this effort.

The Chronic Obstructive Pulmonary Disease (COPD) Foundation Biomarker Qualification Consortium (CBQC) was formed in 2010 as a partnership between the COPD Foundation, pharmaceutical companies, academic experts, patient care groups, and the FDA. One candidate biomarker selected by the CBQC was plasma fibrinogen, a marker of systemic inflammation that is elevated in conditions such as COPD. Systemic inflammation is associated with many of the pulmonary and extra-pulmonary manifestations of COPD, although evidence indicates that not all patients with COPD have elevated concentrations of biomarkers of systemic inflammation. Research also shows that elevated levels of biomarkers such as fibrinogen are associated with a greater risk of adverse COPD outcomes including COPD exacerbations and all-cause mortality.

In a Letter of Intent, the CBQC proposed plasma fibrinogen for two contexts of use in drug development: (1) as an enrichment factor for COPD subjects more likely to experience a COPD exacerbation, and (2) as an enrichment factor for COPD subjects at higher risk for all-cause mortality. These proposed contexts of use reflect the belief that routine assessment of fibrinogen levels in the course of the enrollment of a clinical trial may improve the identification of subjects more likely to experience COPD exacerbations or those who have a higher mortality risk. This enrichment of clinical trial populations with patients who are more likely to experience the outcome of interest during the study period would reduce the number of subjects who need to be enrolled while maintaining statistical power, and decrease both the cost and duration of the trial (due to shorter study enrollment periods).

Methods

A literature review identified potential data sources that contained measurements of fibrinogen and lung function, had available subject-level data on at least 50 patients with COPD, and had outcomes of interest (COPD...
exacerbations and all-cause mortality) over a minimum of 6 months of follow-up. The following five data sources met all criteria and were obtained by the CBQC:

- The National Health and Nutrition Examination Survey III (NHANES III)\(^6\)
- Framingham Heart Study (FHS) Offspring Cohort\(^7\)
- Cardiovascular Health Study (CHS)\(^8\)
- Atherosclerosis Risk in Communities Study (ARIC)\(^9\)
- Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE)\(^10\)

The data were compiled into an integrated dataset by INC Research, and the CBQC partnered with Evidera to assist in the development of a statistical analysis plan (SAP), conduct analyses to support the proposed contexts of use, and prepare the qualification package for submission to the FDA.

Patients aged 40+ who met the GOLD criteria for moderate, severe, or very severe COPD were eligible for inclusion.\(^11\) Prior COPD exacerbation history was available only for patients in the ECLIPSE dataset. Outcomes of interest were moderate and hospitalized COPD exacerbations within 12 months and all-cause mortality within 36 months, and these time periods were chosen to simulate those used in a clinical trial. Fibrinogen was assessed using four hypothetical thresholds: 250 mg/dL, 300 mg/dL, 350 mg/dL, and 400 mg/dL.

### Statistical Analyses

The demographic and clinical characteristics of patients in the integrated dataset (i.e., all five databases combined) as well as in each individual dataset were assessed using descriptive statistics. Kaplan-Meier curves were used to present time-to-event data, with some stratified by history of exacerbations (for analyses conducted using only...enrichment of clinical trial populations with patients who are more likely to experience the outcome of interest during the study period would reduce the number of subjects who need to be enrolled while maintaining statistical power..."

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<table>
<thead>
<tr>
<th>Table 1: Baseline Characteristics of COPD Patients</th>
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<tbody>
<tr>
<td><strong>Total</strong> (n=6,376)</td>
</tr>
<tr>
<td><strong>AGE</strong></td>
</tr>
<tr>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Median (range)</td>
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<tr>
<td><strong>GENDER</strong></td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td><strong>RACE</strong></td>
</tr>
<tr>
<td>Non-white</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Missing</td>
</tr>
<tr>
<td><strong>ETHNICITY</strong></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>Missing</td>
</tr>
<tr>
<td><strong>SMOKING STATUS</strong></td>
</tr>
<tr>
<td>Never</td>
</tr>
<tr>
<td>Former Smoker</td>
</tr>
<tr>
<td>Current Smoker</td>
</tr>
<tr>
<td><strong>FIBRINOGEN LEVELS</strong></td>
</tr>
<tr>
<td>Mean Fibrinogen (SD)</td>
</tr>
</tbody>
</table>
Figure 1: Time to First COPD Exacerbation Within 12 Months, ECLIPSE: Fibrinogen Threshold 350 mg/dL

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Figure 2: Time to Death Within 36 months, All Patients: Fibrinogen Threshold 350 mg/dL

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data from ECLIPSE). Univariate analyses were performed to assess the relationship between clinically relevant covariates and the outcomes of interest. Multivariable Cox proportional hazards models were used to present the association between fibrinogen and COPD outcomes after adjusting for relevant covariates. Finally, analyses were conducted to compare the sample sizes required in hypothetical clinical trials with and without the use of a fibrinogen threshold as part of the inclusion criteria. Confidence intervals presented in these sample size analyses were obtained using bootstrapping procedures.

### Selected Results
A total of 6,376 patients from ARIC, CHS, ECLIPSE, FHS, and NHANES met the inclusion criteria for analyses. The mean age of patients was 63.6 ± 9.8 years (Table 1), the majority (61.9%) were male, and most were either former (47.2%) or current smokers (40.4%). The pooled mean baseline fibrinogen level was 351.7 ± 89.3 mg/dL among COPD participants included in the integrated dataset.

The time to any exacerbation (moderate or hospitalized exacerbation) within 12 months among patients in ECLIPSE is presented in Figure 1. Using a threshold of 350 mg/dL (i.e., “high” is equivalent to fibrinogen levels ≥ 350 mg/dL), 41.4% of individuals with low fibrinogen had an exacerbation within 12 months, compared to 48.3% with high fibrinogen. ECLIPSE subjects with a history of 1 or more COPD exacerbations and high fibrinogen were at higher risk for another exacerbation of any type within 12 months when compared to participants with a history of exacerbations and low fibrinogen (75.6% vs. 70.5%).

Using the same threshold, 6.0% of participants with low fibrinogen in ARIC, CHS, ECLIPSE, FHS, and NHANES had died within 36 months, compared to 13.0% of participants with high fibrinogen (Figure 2). High fibrinogen was associated with an increased risk of death within 36 months (HR: 1.94; 95% CI: 1.62–2.31) among all participants.

Table 2: Sample sizes (95% CI) by fibrinogen levels and hazard ratios based on the number of hospitalized exacerbations over a 12-month time-period for ECLIPSE subjects by history of exacerbation

<table>
<thead>
<tr>
<th>Fibrinogen Level</th>
<th>Total N</th>
<th>N (%) of Subjects with Hospitalized Exacerbation within 12 Months</th>
<th>Total Sample Size by Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR=0.70</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Difference Over No Threshold, n (%)</td>
</tr>
<tr>
<td>Without a History of Exacerbation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Threshold</td>
<td>1,114</td>
<td>94 (8%)</td>
<td>4,528 (3,590-5,580)</td>
</tr>
<tr>
<td>&gt; 250</td>
<td>1,082</td>
<td>94 (9%)</td>
<td>4,418 (3,476-5,384)</td>
</tr>
<tr>
<td>&gt; 300</td>
<td>973</td>
<td>87 (9%)</td>
<td>4,348 (3,474-5,318)</td>
</tr>
<tr>
<td>&gt; 350</td>
<td>718</td>
<td>70 (10%)</td>
<td>4,078 (3,144-5,266)</td>
</tr>
<tr>
<td>&gt; 400</td>
<td>441</td>
<td>49 (11%)</td>
<td>3,806 (2,782-5,088)</td>
</tr>
<tr>
<td>With History of Exacerbation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Threshold</td>
<td>1,004</td>
<td>241 (24%)</td>
<td>1,338 (1,198-1,490)</td>
</tr>
<tr>
<td>&gt; 250</td>
<td>985</td>
<td>239 (24%)</td>
<td>1,328 (1,202-1,458)</td>
</tr>
<tr>
<td>&gt; 300</td>
<td>901</td>
<td>230 (26%)</td>
<td>1,268 (1,142-1,402)</td>
</tr>
<tr>
<td>&gt; 350</td>
<td>716</td>
<td>199 (28%)</td>
<td>1,182 (1,058-1,346)</td>
</tr>
<tr>
<td>&gt; 400</td>
<td>488</td>
<td>149 (31%)</td>
<td>1,090 (954-1,248)</td>
</tr>
</tbody>
</table>

“These analyses provide evidence from a range of heterogenous longitudinal datasets that elevated levels of fibrinogen among subjects with COPD are associated with outcomes commonly used as endpoints in clinical trials...”
Table 2 presents the difference in sample size required for a clinical trial with hospitalized exacerbations within 12 months as an outcome when a fibrinogen threshold is applied. For example, at a hazard ratio of 0.70, the sample size of each arm (treatment and control) among patients who had at least one previous exacerbation could be reduced by 5% using a threshold of 300 mg/dL, by 12% using a threshold of 350 mg/dL, and by 19% using a threshold of 400 mg/dL. Likewise, the sample size of each arm in a trial of mortality within 36 months and hazard ratio of 0.70 (Table 3) could be reduced by 3% using a threshold of 300 mg/dL, 8% using a threshold of 350 mg/dL, and 20% using a threshold of 400 mg/dL, among patients with a history of at least one COPD exacerbation.

**Conclusion**

These analyses provide evidence from a range of heterogenous longitudinal datasets that elevated levels of fibrinogen among subjects with COPD are associated with outcomes commonly used as endpoints in clinical trials, including COPD exacerbations within one year and death within three years. Data from the ECLIPSE study indicate that this relationship also holds among the subset of patients who have a history of exacerbations, and these patients typically form the subject pool for COPD clinical trials assessing the impact of an intervention on COPD exacerbations. Further analyses indicate that the use of a fibrinogen threshold during the enrollment phase of a clinical trial would permit a reduction in the sample size of each study arm, while maintaining the statistical power of that trial.

On July 6, 2015, the FDA qualified plasma fibrinogen as a prognostic biomarker for enrichment of clinical trials in COPD. This qualification permits the use of fibrinogen for clinical trial enrichment in submissions for investigational new drug applications, new drug applications, and biologics license applications without additional review from the FDA to reconfirm the suitability of fibrinogen as a biomarker. The successful qualification of plasma fibrinogen as a prognostic biomarker for use in COPD drug development is an important step in the effort to facilitate clinical trials of novel therapies and demonstrates the value of a public-private consortium working with regulatory officials.

For more information, please contact Jason.Simeone@evidera.com or Nancy.Leidy@evidera.com.
REFERENCES


Introduction
Many healthcare systems have the objective of not only improving health outcomes but also reducing health inequities. This is reflected in the decision factors considered in Health Technology Assessment (HTA). However, whereas efficiency is often precisely defined and formally measured, equity considerations are generally incorporated into HTA through committee deliberations. The lack of rigor and transparency associated with such deliberative approaches may very well lead to inconsistent and inadequate considerations of equity in HTA.

Several approaches have been proposed to redress this imbalance. Most prominently, it has been suggested that willingness to pay thresholds be weighted to reflect health equity considerations such as baseline burden of disease. This approach is adopted in the Netherlands, and is currently the favored method used by NICE in their consultation on value-based assessment.

Multi-criteria decision analysis (MCDA) is an alternative approach receiving an increasing amount of attention. MCDA is an umbrella term that refers to a set of analytical methods and techniques to support decision-making and the evaluation of alternatives on multiple, often conflicting, criteria and objectives. Indeed, MCDA has the potential to bring a number of benefits to healthcare decision making. It offers techniques that can value health technologies in a manner compatible with traditional approaches to HTA. One particular benefit is its ability to formally define, measure, weight, and incorporate health equity considerations into a comprehensive evaluation of health technologies.

The objective of this article is twofold: to review and illustrate the use of MCDA to incorporate health equity into HTA, and to identify good practices in doing so.

Current use of MCDA to capture health equity benefits
As their familiarity with MCDA grows, healthcare decision-makers and researchers are increasingly acknowledging its potential to improve decision-making. Consequently, there has recently been an increase in the number of publications on the implementation of MCDA in healthcare. Among these, there are several examples
of MCDAs that incorporate health equity criteria, such as severity of disease or access to effective treatment. More specifically, of those MCDAs designed to support healthcare resource allocation decisions, 53% included severity of a disease and 42% included access to an effective treatment.\textsuperscript{6}

This interest is not confined to methodological curiosity. HTA agencies are piloting and implementing MCDA. In Germany, the Institute for Quality and Efficiency in Health Care (IQWiG) has piloted the use of two types of MCDAs — conjoint analysis and the analytical hierarchy process — to weigh clinical endpoints and generate efficiency frontiers based on aggregated outcomes.\textsuperscript{10, 11} The Lombardi region of Italy has adopted an MCDA framework for HTA.\textsuperscript{12}

Table 1 illustrates how health equity is incorporated in an MCDA assessment of hospital medical technologies in Hungary. Between its introduction in 2010 and 2013, 14 applications were assessed using this MCDA. Criteria and their weights were established by a committee comprising the healthcare financing agency, the Ministry of Health, clinical experts, and health economists. Weights were determined by allocating 100 points across the criteria to reflect their relative importance. The criteria and weights were submitted to other stakeholders for validation. Several equity concepts are incorporated into the Hungarian MCDA, including numbers of patients, access to treatment, and severity of disease. In combination these factors account for 30% of the weights attached to criteria.

The MCDA technique adopted in Hungary is an additive value approach, as is the case for most MCDAs for HTA developed to date. Such additive models are commonly used as they are relatively easy to understand and apply. They do, however, raise several methodological concerns. This is illustrated in the next section.

### Good practice when using MCDA to incorporate health equity into HTA

Additive value models of the type applied to support HTA require a number of analytical assumptions. Among these assumptions is the requirement that criteria are preferentially independent – the strength of preference for the performance of an option on a given criterion should not depend on its performance on another criterion.\textsuperscript{14} However, incorporating certain health equity considerations, such as severity of disease, into additive value models often ignores this requirement, as the health outcome criterion is not preferentially independent of the severity of disease criterion.

This observation is the basis for a criticism of the way that the quality adjusted life year (QALY) is currently used in HTA. Cost-utility analysis invariably assumes that QALYs

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Points (weight)</th>
</tr>
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<tbody>
<tr>
<td>1. Health care priority</td>
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</tr>
<tr>
<td>I.1. Public health programs</td>
<td>6</td>
</tr>
<tr>
<td>I.2. Health policy priority</td>
<td>7</td>
</tr>
<tr>
<td>I.3. Aggregated health benefit</td>
<td>7</td>
</tr>
<tr>
<td>II. Severity of disease</td>
<td>15</td>
</tr>
<tr>
<td>II.1. Life-threatening disease — acute</td>
<td>13-15</td>
</tr>
<tr>
<td>II.2. Life-threatening disease — chronic</td>
<td>10-12</td>
</tr>
<tr>
<td>II.3. Not a life-threatening disease — acute</td>
<td>8-9</td>
</tr>
<tr>
<td>II.4. Not a life-threatening disease — chronic</td>
<td>6-7</td>
</tr>
<tr>
<td>III. Equity</td>
<td>15</td>
</tr>
<tr>
<td>III.1. Number of patients</td>
<td>8</td>
</tr>
<tr>
<td>III.2. Availability Access</td>
<td>7</td>
</tr>
<tr>
<td>IV. Cost-effectiveness, quality of life</td>
<td>30</td>
</tr>
<tr>
<td>IV.1. ICER (incremental cost-effectiveness ratio)</td>
<td>15</td>
</tr>
<tr>
<td>IV.2. Health benefit per patient</td>
<td>15</td>
</tr>
<tr>
<td>V. Aggregated budget impact</td>
<td>10</td>
</tr>
<tr>
<td>VI. National and international reputation</td>
<td>10</td>
</tr>
<tr>
<td>VI.1. Opinion of medical college</td>
<td>3</td>
</tr>
<tr>
<td>VI.2. International application</td>
<td>3</td>
</tr>
<tr>
<td>VI.3. Grading of evidences related to the procedure under consideration</td>
<td>4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>100</strong></td>
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</table>
have the same value; an approach often summarized in the saying ‘a QALY is a QALY is a QALY’. However, this is contrary to the argument that the value of a health outcome is a function of baseline health, among other things. Figure 1 shows Nord’s proposed health value function, which illustrates how we might expect the value of a health outcome to depend on baseline health.

In the remainder of this section, we illustrate the challenges of using the additive models in the presence of non-independent criteria, assuming that our objective is to capture the value judgments reflected in Figure 1. Table 2 illustrates the calculations involved in applying the type of additive model commonly used when applying MCDA to HTA. A simple two-criteria MCDA is used in the illustration. The first criterion is health outcome, measured as life expectancy in QALYs. The second criterion is baseline health, which we use as a proxy for equity considerations. This is measured in discrete categories, also defined in QALYs, with decreasing severity. The analysis contains 11 hypothetical treatments that have 0-10 QALY health outcomes with different baseline health profiles (categories 0–9 QALYs).

The first step in the MCDA is to convert performance on each criterion into preference scores on a common 0-1 scale, representing the perceived value of these performances, which enables the comparison and subsequent aggregation of the measures. We assume a linear transformation for both the health outcome and the baseline health criterion, for simplicity of illustration, although we appreciate different disease contexts may call for different shapes.

The second step is to determine value trade-offs, or to quantify how each criterion is prioritized using weights. We assume one unit increase in health outcome to be 2.7 times more important than one unit decrease in baseline health, meaning that the weight of health outcome must be $3 = \frac{10}{9} \times 2.7$ times the weight of baseline health. The normalized weights are then 0.75 and 0.25, and an overall value for each treatment can then be obtained by aggregating these scores and weights. For instance, the value of the fourth treatment in Table 2 using the additive function is $0.42 = 0.75 \times 0.30 + 0.25 \times 0.78$.

The challenge with using additive value functions in the presence of non-preferentially independent criteria can be illustrated by comparing the health value function generated with the additive value model (Figure 2) with that hypothesized in Figure 1. In contrast to the

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<tr>
<th>Treatment</th>
<th>Health Outcome</th>
<th>Baseline Health</th>
<th>Additive VF</th>
<th>Multiplicative VF</th>
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<tr>
<td></td>
<td>QALYs</td>
<td>Normalized Score</td>
<td>QALY Category</td>
<td>Normalized Score</td>
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<td>1.00</td>
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<td>0.00</td>
</tr>
</tbody>
</table>
non-linear function in Figure 1, the additive value function in Figure 2 is broadly linear.

In the presence of a lack of independence between criteria, good practice is to either adopt a multiplicative model or to combine the interacting criteria into a single criterion. Multiplicative models give different values to health gains for different levels of baseline health. Table 2 illustrates this in the form of a ‘multiplicative factor’, which values each QALY outcome differently depending on the baseline health level. For instance, the value of the fourth treatment in Table 2 using the multiplicative function would be $0.53 = 1.78 \times 0.30$, where 1.78 represents the multiplicative factor applied to the health outcome due to the severity of the disease. Figure 3 reports the result of this multiplicative model which displays similar non-linear characteristics to Nord’s hypothesized function (Figure 1).

The multiplicative function in Figure 3, while having similar characteristics, does not have the exact same form as the hypothesized function in Figure 1. This is because of the exact multiplicative factors applied in the multiplicative function, which were assumed for the sake of illustration. These should be elicited from stakeholders, rather than being assumed by the researcher. The recommended approach for eliciting these value judgments is illustrated in Figure 4, which requires stakeholders to provide a value for the same QALY gain dependent on the baseline disease severity. In this instance, we are determining the value (on a 0-100 scale) of three levels of QALY gain for three levels of disease severity, where a high QALY gain from a point of high disease severity is valued at 100. The result is effectively a new criterion, which can be scored on nine levels, where each level is a function of two attributes: severity of disease and health outcome.

The implications of these observations will depend on the decision problem the MCDA is designed to support. If the purpose is to rank interventions, such as when supporting clinician-patient shared decision-making, the additive model may be acceptable. If, however, the objective is to value interventions, such as when undertaking HTA or informing pricing decisions, a more sophisticated approach would be needed, such as either the multiplicative method or the additive method with combined criteria as described earlier.

**Conclusion**

MCDA has the potential to bring increased transparency, consistency and accountability to healthcare decision making. However, current applications of MCDA fail to adequately capture social value judgments, risking providing spurious recommendations to decision makers. We have illustrated this with the example of health equities. This illustration is based on an assumption that the true health value function corresponds with that hypothesized by Nord. This assumption requires further validation. However, in the meantime this serves to raise important questions about the appropriateness of the current use of additive value function in healthcare. We welcome the increased interest in MCDA, though caution that more care is needed, and that the use of MCDA is accompanied by a more sophisticated methodological discussion than is currently the case.

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Researchers familiar with patient-reported outcomes (PROs) may find that the transition to working with clinician-reported outcomes (ClinROs) is not as seamless as expected. Though both types of outcomes are required to meet the same criteria to be submitted as evidence to support a label claim (“well-defined and reliable”), the details involved in validating a ClinRO for use can be a bit more entangled than those involved with a PRO. One piece of the validation process that can often prove challenging is the assessment of inter-rater (inter-clinician) reliability or agreement.

Clinical trial researchers are looking for measures with as little measurement error as possible, hence a great deal of emphasis should be placed by measure developers on understanding all the potential sources of error in order to minimize or eliminate them. With ClinROs there is a new source of error in the measurement process: the “clinician.” The FDA glossary describes Clinical Outcome Assessments (COAs), which include ClinROs, as “any assessment that may be influenced by human choices, judgment, or motivation and may support either direct or indirect evidence of treatment benefit. ... COAs depend on the implementation, interpretation, and reporting [emphasis added] from a patient, a clinician, or an observer.”¹ The definition of ClinRO in the same glossary expands a bit on this with reference to the special aspects of potential human error brought in by clinicians:

“Clinician-reported outcome (ClinRO) — A ClinRO is based on a report that comes from a trained health-care professional after observation of a patient’s health condition. A ClinRO measure involves a clinical judgment or interpretation of the observable signs, behaviors, or other physical manifestations thought to be related to a disease or condition [emphasis added].”¹

All of this is to catalog the many potential sources of human error found in all COAs, PROs, and ClinROs alike (Table 1). Given the inclusion of the clinician in the measurement process, ClinROs include some unique sources of potential error which developers have the opportunity to evaluate in examining inter-rater/-clinician agreement. Determining how much a ClinRO measurement could vary, simply as a result of the clinician is who is using the ClinRO, is integral to the ClinRO’s measurement properties. The degree to which internal and environmental variables for a given individual patient add unwanted measurement error in PROs is generally quite difficult to evaluate, though an attempt is often made to assess the effects of transient factors in examining test-retest reliability. However, with ClinROs additional access to the process is afforded, thus in developing a ClinRo, it is essential to evaluate how much clinicians tend to agree (or disagree) on a given assessment. There are many characteristics of good measurement that must be shown in addition to inter-rater reliability, including intra-rater reliability and validity. Assessment of agreement between clinicians establishes both reliability and generalizability. Beyond understanding the error sources, demonstrating high agreement among clinicians is an important part of a needed argument in any study for extending the given results beyond a particular study sample, i.e., the generalization justification. This work is also foundational to validity work included in any label claim for a clinician-reported outcome, because if clinicians cannot agree about what they report concerning a given patient, one can hardly consider such information valid.

As with PROs there is the same basic set of frameworks in which one can work on the reliability issue:

“Assessment of agreement between clinicians establishes both reliability and generalizability.”
generalizability theory, classical test theory, and modern measurement theory including various modeling approaches such as latent trait modeling. Generalizability theory, while infrequently used, allows one to expand the number of dimensions along which reliability can be assessed. It provides a natural way of assessing both intra- and inter-clinician reliability, providing some insights into the sources of measurement “unreliability” and allowing for greater efficiency in study design. Classical test theory methods (Cohen’s kappa, intra-class correlations, etc.) are most often used, though the other frameworks provide certain advantages or benefits. Modeling approaches can provide a deeper understanding of the sources of variability or bias in clinician reports, which can in turn be used in clinician training to increase the reliability of ClinROs.

When it comes to using classical test theory to assess the question of clinician agreement, or consistency (aka inter-rater, inter-judge, or inter-observer reliability, and “intra-“ forms of these as well), researchers face a bewildering array of statistics or variants designed for this purpose. Though most of these statistics have been in use for some time, design flaws or, at least, complications have been found in some cases of which researchers may not be aware. One of the more popular statistics, the Cohen’s kappa has the potential for several problematic issues including biased estimates and paradoxical results. Moreover, these statistics come in various forms from which researchers need to select the appropriate one. There is not a single kappa or intra-class correlation (ICC), but rather several versions that vary according to the data collection design and proposed purpose of the measure. McGraw and Wong (1996) report five possible ICC statistics for individual scores and five more for combined scores. Those unfamiliar with these statistics and their potential problems may find themselves confused by results or making mistaken claims.

To correctly assess the inter-clinician reliability of the proposed ClinRO, the researcher will need to carefully consider and navigate a series of issues. To start with, the researcher will need to have a clear idea of how the measure will be used. Is this a measure that will be used for assessment in clinical practice, or is this measure intended for use in group comparisons in clinical trials? The researcher needs to select the agreement statistic that is most appropriate for assessing reliability or risk an endpoint failure. In most cases for clinical trial use, the group comparison use is all that is expected, thus using a statistic fitted to that purpose will be to the researchers advantage. The nature of the ClinRO itself needs to be considered, namely the level of measurement (nominal, ordinal, interval, continuous) it affords. Again, there are different statistics designed for different levels of measurement; not all are appropriate for every use. Another important issue to understand is what criteria your reviewers will require your measure to meet? Will you need to pass a statistical test (e.g., a test of the agreement level surpassing some value) or meet a certain descriptive criterion, i.e., show a level of agreement with some degree of precision? Some thought needs to be given to justify this choice when it is not explicitly defined. Finally, study design also needs to be carefully considered in choosing a statistical approach. In fact, if you have early input into the study design, it is very useful to be able to consider the needs of the statistical approach when designing the study. The relevant design concerns are the numbers of patients and clinicians, whether the selection is random in either or both cases, and the plans for study generalization. The question of minimum sample size and best design in view of various costs will inevitably arise in study planning. In many cases, there are methods for determining optimal design parameter values. The important thing to understand is

**Table 1: Sources of Variability and Bias: PRO Versus ClinRO**

<table>
<thead>
<tr>
<th>Sources of variability and bias in target experience</th>
<th>Sources of variability and bias in reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRO</strong></td>
<td><strong>ClinRO</strong></td>
</tr>
<tr>
<td>transient effects</td>
<td>All the above plus:</td>
</tr>
<tr>
<td>learning effects</td>
<td>• clinician effects</td>
</tr>
<tr>
<td>real change</td>
<td>• clinician x patient interaction effects</td>
</tr>
<tr>
<td>patient's reporting bias</td>
<td>All the above</td>
</tr>
<tr>
<td>interaction with the reporting instrument</td>
<td></td>
</tr>
</tbody>
</table>
that the choice of agreement statistic will be constrained by the design, and some statistics are less desirable for a given design. If your statistical plan includes a specific statistic, it needs to have a matched design.

While most research has traditionally used the classical test theory approaches to establishing adequate agreement among clinicians, more revealing modeling approaches have been developed (latent trait models and latent class models, among others). Uebersax (1992) provides a brief overview of select models that offer certain advantages over the classical approaches. A major weakness of all the classical statistics is that they do not identify the source of disagreement among clinicians where there is less than perfect agreement, and therefore afford little help in trying to improve a ClinRO while under development. Modeling approaches address this weakness. Agreement modeling is able to analyze undifferentiated aspects of the reporting process thereby identifying various sources of disagreement, whether it is overall reporting-level bias, different use of response categories, or just general measurement error which is responsible for the disagreement. This provides the researcher with important information which can often be used to target appropriate revisions to a ClinRO. As a result, modeling approaches provide a clear path to improving the performance of a ClinRO if used early in the development cycle.

ClinROs have come to play an important role among the broad group of COAs. In fact, they are probably much more widespread than PROs in many therapeutic areas where patient insight into their own condition is frequently in doubt (e.g., dementia). Given that importance, care needs to be exercised in the psychometric evaluation. As the reader can see, there are many decisions to be made in assessing inter-clinician agreement in ClinRO submissions. There is no single off-the-shelf approach one can use in every case. It would take a monograph-length tutorial to do justice to all of them, so no attempt has been made to do this here. Nonetheless, this article can serve to raise researchers’ consciousness of the complications, alert researchers to potential pitfalls in the process, and increase their awareness of the role experimental design issues play in such appraisals. The statistical approach to assessing inter-clinician agreement needs careful consideration within an overall validation plan to avoid costly mistakes or schedule slippage—outcomes that can occur when not enough data were collected to support your claim, or if analyses need to be redone because regulators indicate the wrong statistical approach was used.

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ACKNOWLEDGEMENTS
I would like to acknowledge the contributions made to this article by William Lenderking, PhD, Senior Research Leader; Dennis A. Revicki, PhD, Senior Vice President and Senior Research Leader; and Karin Coyne, MPH, PhD, Vice President Research, Outcomes Research, Evidera.

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Early Network Meta-Analyses (NMAs): Filling a Need in Clinical Trial Designs and HTA Submissions

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Please note this is an update of an article which appeared in the May 2015 issue of The Evidence Forum and includes authors inadvertently left off of the original article.

Stakeholder demands for evidence on new health treatments and technologies are increasing, and these demands are progressively more complex. As a result, companies must think about evidence requirements for reimbursement decisions, as well as regulatory approval, earlier in the development process. One crucial piece of evidence that private and national payers expect to see when evaluating a new treatment within a given patient population is results from comparative studies, ideally from head-to-head randomized controlled trials (RCTs) comparing the new treatment with the current standard of care. In the absence of head-to-head RCTs meeting these requirements, payers (such as the National Institute for Health and Care Excellence [NICE]), often expect to see a network meta-analysis (NMA) that collates and combines results across studies to evaluate the clinical value of the new technology. However, NMAs are not a panacea and cannot overcome the absence of good clinical evidence. In some health technology assessment (HTA) submissions to NICE, NMAs were either not feasible or criticized to some extent because the manufacturer’s clinical trial design made it impossible to compare the drug with current standard of care in an evidence network.1 One solution to this problem is to perform an NMA earlier in the drug development process. An early NMA can inform Phase 3 trial designs by identifying relevant patient subpopulations, comparators, outcomes, and timepoints for data collection, and ensuring that the Phase 3 trial will connect to other studies in the network.

Network Meta-Analysis

An NMA is based on evidence from multiple RCTs of the treatment of interest, including both direct comparisons (trials that directly compare two or more treatments of interest) and indirect comparisons (multiple trials that each compare a treatment of interest to a common comparator). The validity of both types of comparisons is based on an “exchangeability assumption”; that is, they assume that the true effects of each treatment relative to a given comparator are “exchangeable”, or comparable, across trials, even trials that did not examine a given treatment. It is important to note that the validity of this assumption can be limited due to heterogeneity among trials (e.g., differences in patient population, interventions, outcome definitions, timepoints for data collection, etc.), and the risk of a violation increases when a large number of “links” in a network is required to connect two comparators of interest.

For the drug evaluation process, an early NMA can fill an important need by providing information about both the competitive landscape and the evidence landscape of the treatment. This information can then be used to help ensure the design of the clinical trial for the new treatment is optimal to provide strong support for an HTA submission. Specifically, an NMA can help with the definition of the target patient population for the...
Phase 3 trial and identify a situation in which evidence for different treatment combinations are in separate evidence networks.

Figure 1 shows an example where there were two populations of interest. In the Figure, the client’s trials are Trial 3 and Trial 4. The patient population in Trial 3 was previously treated patients; Trial 4 was performed on treatment-naïve patients.

In Trial 4, the product was compared to placebo, although no placebo-controlled clinical trial had ever been published. The intent was to compare the product (D) to treatments A and C in the treatment-naïve population. Unfortunately, the only trial providing a network link between the competitive treatments of interest (A and C) and the product (D) was Trial 3, performed in a population of previously treated patients. To perform an NMA in this situation would require assuming that relative rates for the outcome were identical in the previously treated and untreated patient populations – highly unlikely, and unlikely to be accepted by clinicians or payers. Thus, no NMA was possible for the treatment-naïve population. If an early NMA had been performed, the situation would have been clear and the client could have elected to use the same comparator (B) in Trial 4 that they had used in Trial 3, linking the network for both treated and untreated patients.

The Perspective from NICE

NICE is an independent government body that is dedicated to identifying the most effective ways to prevent, diagnose, and treat disease and to ensure quality and value for money for the UK National Health Service (NHS). When conducting technology appraisals for new healthcare technologies, NICE compares the clinical and cost effectiveness of the proposed technology to the current established practice in the NHS. Once again, the preferred evidence is a head-to-head RCT. When no head-to-head RCT is available, an NMA is acceptable, if appropriate, for comparisons, along with a detailed description of the methodology used. The NICE technology appraisal committee expects to see systematic identification of studies; justification for the inclusion and exclusion of selected studies; analysis of the heterogeneity between studies; and sensitivity analyses exploring the impact of including or excluding potentially heterogeneous studies. Additionally, NICE also requires details on how the NMA results are used in the economic analyses presented in support of the product, in addition to the reference case analysis. Before undertaking any pivotal trials, companies should plan accordingly to identify evidence that is already available, ensuring that the trial program design facilitates links with the available evidence. Comparators that may become available at a later date should also be considered, as well as how their study designs may affect an NMA at the time of a future technology appraisal.

As shown in Figure 2, there has been a recent increase in the proportion of criticized NMAs cited in submissions to NICE. Common issues include: inadequate searches for studies; missing key studies; lack of transparency about how study inclusion and exclusion decisions were made; choices of population, comparators, and outcomes; inadequate or poor reporting; and errors in statistical analysis. Having knowledge of these issues with the evidence base earlier in the process would allow investigators the opportunity to address these challenges and plan for a more complete submission. For example, an early NMA may facilitate the identification of relevant outcomes and provide the knowledge to

Figure 2: Percentage of NMAs Cited in Submissions to NICE that were Criticized

![Figure 2: Percentage of NMAs Cited in Submissions to NICE that were Criticized](chart.png)
ensure that outcome definitions are matched to other available evidence, and that the outcomes are measured at the same timepoints to be truly comparable. Even if, ultimately, an early NMA does not or cannot change the population, outcomes, or comparators in any Phase 3 trials conducted, companies are still further along by knowing where they stand earlier in the process.

The following example describes a situation where a manufacturer used an early NMA to understand how the available evidence for an NMA from an HTA perspective would fit with regulatory requirements (in this example, specifying an expected endpoint). The manufacturer performed an NMA before Phase 3 to get a sense of the competitive landscape and understand the available evidence. The result of the literature review of RCTs in endometriosis is the extensive network of 27 clinical trials shown in Figure 3. Most of the trials used the Modified Biberoglu and Behrman scale to report symptoms. However, the U.S. Food and Drug Administration (FDA) recommends that symptoms of endometriosis be measured by the daily pain level reported by the patient – a measure that none of the 27 RCTs reported. The drug manufacturer could use the results of this early NMA to ensure that the expectations of both regulatory bodies and payers are met.

**Conclusion**

When head-to-head RCTs are not available for the treatment under consideration, early NMAs can potentially fill a need when planning for HTA submissions. In many cases, a non-optimal trial design can make it difficult to demonstrate the full clinical value of a new treatment. An NMA performed before designing a Phase 3 trial, or earlier if conditional reimbursement is sought, may provide improved insight and direction for manufacturers to better demonstrate the clinical and economic value of a new product. Performing an NMA early in the clinical trial design process can not only help determine the optimal population, subpopulations, comparators, and outcomes to investigate, but the resulting information can also help the manufacturer explain and justify the design choices made for the clinical trial in support of an HTA submission.

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**REFERENCES**


Introduction
The importance of real-world data both in drug development and post product launch is well known. However, what needs increased recognition is that the quality and ultimate utility of a study using real-world data is highly dependent on the information available in the data source. Commonly used, real-world data sources include electronic medical records and administrative health insurance claims data, but in a world where there are often many therapeutic options for a disorder, there is a pressing need to obtain detailed data on a disease in order to provide insights into unmet need and treatment effectiveness. As such, there is a shift occurring from using routinely collected data to disease-specific data sources.

What are disease-specific data sources?
Disease-specific data sources are databases, registries, or studies using observational methods to evaluate a specific population of people with a disease. Standardized information is collected about the patients, and it may be cross-sectional or longitudinal in nature. Disease-specific data sources are generated for the purpose of observational data collection that can be used for a specific research agenda, including the monitoring of disease natural and treated history, patient outcomes, and the study of best practices in care or treatment. They may pursue a specific, focused research agenda, collecting data for a limited time to answer a specific research question, or may collect data on an indefinite basis to answer a variety of existing and emerging research questions. The sources may be organized and operated in a variety of forms and formats.

In this article, we will explore the advantages and disadvantages of using disease-specific data sources in real-word studies, using two case studies; multiple sclerosis, a specific neurological disease with a recent sea change occurring in disease treatment; and cancer, a highly prevalent disease appearing in many different forms and a corresponding vast therapeutic armamentarium.

Case Study - Multiple Sclerosis
Multiple sclerosis (MS) is the most common neurological disorder affecting young adults in North America and Europe. About 85% of patients present initially with relapsing-remitting MS (RRMS), characterized by recurrent episodes of neurological dysfunction interspersed with periods of lack of apparent disease activity.¹ At present, there are 13 disease-modifying therapies (DMTs) approved by the U.S. Food and Drug Administration (FDA)² and 11 DMTs approved by the European Medicines Agency (EMA)³ for the treatment of RRMS, with new treatment options emerging each year.

The clinical trials that led to the approval of these treatments for RRMS are recognized for their limitations in terms of providing data on efficacy rather than effectiveness. They further lack the ability to provide more general epidemiologic data about MS, for example disease incidence; most frequent reasons for hospitalization in patients; and major drivers of cost of care.

Routinely collected data, that is administrative data collected by insurance companies (e.g., sickness fund data from Germany) or electronic medical records (e.g., the Clinical Practice Research Datalink [CPRD] in the United Kingdom), provide the mainstay for real-world...
data analyses. There are a number of benefits to using such data - namely they are readily available and relatively inexpensive. However, there are a number of limitations with routinely collected data. In Europe there is a lack of good quality and sufficiently representative data in many countries. For data sources that do exist, their biggest deficiency is the incompleteness of data. Data sources generally do not include different types of care - they may be focused on primary care or the hospital sector, but rarely cover all the different settings that play a role in medical treatment. This is becoming more important for MS as the availability of newer monoclonal antibody therapies increases the number of treatments given in secondary care, which is not captured in primary care medical record data such as CPRD. Routinely collected data also lack clinical detail, for example information on disease severity measures such as the widely used Expanded Disability Status Scale (EDSS) or magnetic resonance imaging (MRI) results. The coding for identifying patients generally will not allow patients with different forms of MS to be distinguished. Clinical data are critical for analyses of patient outcomes and are a key determinant of prescribed treatment, so missing this information restricts the analyses that can be done.

One way of obtaining more in-depth data on patients with MS is to use a disease-specific data source. Examples of disease-specific data sources in MS include the European Database for Multiple Sclerosis (EDMUS), the Swedish National MS Registry, the Danish National MS Registry, and the global MS Registry (MSBase).4

Looking at one of these data sources provides an illustration of the data available in comparison to general population data sources. MSBase is a longitudinal online registry and is open to any neurologist worldwide to collect data on MS patients. It is registered as a not-for-profit organization in Australia. To initially register a patient on the database, a minimum set of data are needed that encompasses MS course, diagnosis date, EDSS score, paraclinical tests (e.g., MRI), relapse dates, and treatment dates. Further, data entry for at least an annual follow-up visit is required for each patient.5 Clearly, therefore, this data source fills some, but not all, of the clinical and treatment data gaps present in routinely collected data.

"Data sources generally do not include different types of care - they may be focused on primary care or the hospital sector, but rarely cover all the different settings that play a role in medical treatment."

Figure 1: All General Cancer Registries Combined (n=99)

Starting year of the CR and cumulative rate of recording of stage (dotted red line) and treatment data (solid/green line) in population-based cancer registries in Europe ordered geographically.
Case Study – Cancer

Cancer is a major public health problem in the United States (U.S.), in Europe and in many other parts of the world. It is currently the second leading cause of death in the U.S.\(^4\) and in Europe\(^7\) after cardiovascular disease.

In the area of oncology, routinely collected data by insurance companies or electronic medical records similar to CPRD, despite some advantages, have certain limitations, which as for MS are mainly related to the absence of certain data. The most important data gaps are:

- **clinical indicators**: e.g., stage, ECOG (electrocortico-cography), histology, cytology, morphology

- **medical treatment**: as oncology treatment is mostly hospital-administered, data on treatments are absent from the majority of general datasets. The reasons for this is either due to the fragmented nature of the datasets (e.g., covering only primary care) or the application of DRG systems that would not allow the identification of individual drugs given within the hospital setting. Subsequently any information about the duration of treatment, treatment cycle, reasons for treatment discontinuation, and response to treatment is also absent.

- **adverse events**: due to the coding system used for diagnosis of certain conditions (i.e., usually International Classification of Diseases - 9 or 10), specific adverse events are not appropriately recorded (e.g., nausea, vomiting, or other probable adverse events without a respective ICD diagnosis code).

The limitations that stem from the non-availability of certain variables affect all types of studies in the area of oncology: treatment pattern, resource utilization, and burden of illness studies. Epidemiological studies are also affected. Over recent years, population-based data are increasingly used to estimate survival in different cancer populations. However, survival reflects not only treatment but also prognostic factors, such as stage at diagnosis, histological type, and other characteristics of the disease. In the absence of these factors, the reasons for any variations in survival observed cannot be properly identified. Moreover, in the area of oncology the value equation for an oncology product may also be enhanced by demonstrating the impact of therapy in specific patient subgroups, for example non-responding patients.

Looking at the list of recently approved haematology oncology drugs by the FDA, it becomes evident that such evidence is convincing to regulators and payers who seem willing to offer therapies to the patient
subpopulations most likely to benefit from therapy. Therefore, the availability of data on medical treatments and key clinical oncology indicators is paramount in the analysis of patient outcomes.

**Cancer Registries**

Cancer registries have a long history with the first attempts made in the early 1900s in different countries to estimate the number of new and existing cancer cases in given populations. Cancer registries can be grouped into three types: 1) facility-specific registries that collect information about patients diagnosed and treated at a specific facility; 2) specialty registries that only collect information on specific types of cancer (e.g., paediatric cancers); and 3) central cancer registries that collect information about cancer patients in a specific geographic area (country, region, etc.).¹ The main purpose of existing registries is to develop intelligence to monitor and drive improvement in prevention, standards of cancer care, and clinical outcomes of cancer patients. However, the intended purpose of each registry might differ, and this is what defines the necessary properties of the data to be collected. The Cancer Outcomes and Services Dataset (COSD) in the United Kingdom is the national dataset for reporting on cancer in the National Health Service in England. The dataset includes comprehensive data on patient demographic characteristics but also cancer specific data, i.e., morphology, cytology, white blood cell count, platelet count, performance status, whether a patient participates in a clinical trial, tumour-node-metastasis staging classification procedures performed, and patient death details. In addition to core data collected, the dataset also includes cancer-type-specific information.

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**Real-world data in its various forms – ... have an important role to play in the evaluation of epidemiology and burden of disease, treatment patterns, compliance, persistence, and health outcomes of different treatments.**

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For example for breast cancer, additional information is collected on clinical assessment results, mammogram results, Nottingham Prognostic Index (NPI) Score, ASA score, invasive grade, tumour size, Human Epidermal Growth Factor Receptor 2 status, cytology, and biopsy results. Although data on specific treatments received are incomplete, these data provide a wealth of cancer-specific information that is lacking from administrative datasets. However, the nature of each cancer database may vary significantly. The Swedish cancer registry for example, provides detailed information on cancer incidence, mortality and prevalence. The site of the tumour, histological type, basis and date of diagnosis, and stage are being collected at an individual level along with information on patient’s death. However, further clinical and treatment data are not available. The amount of data registries collect is increasing with time (see Figure 1) due to the increased awareness of the importance of such data (see Figure 2).

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**Table 1: Advantages and Disadvantages of Disease-Specific Data Sources**

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focused study population</td>
<td>Limited study population – generalizability only for that specific group of patients</td>
</tr>
<tr>
<td>Specific and detailed clinical information: • disease severity measures • disease specific treatment</td>
<td>No comparator group (e.g., individuals without disease or with other disease[s])</td>
</tr>
<tr>
<td>Study design selected according to the natural history of the disease (e.g., time between follow-up evaluations)</td>
<td>Differences between different datasets. Feasibility assessment required for data content and quality</td>
</tr>
<tr>
<td>Patient subgroups analysis based on various disease-specific indicators</td>
<td>Cost data is not available</td>
</tr>
<tr>
<td>Only feasible method to study patients with rare diseases</td>
<td>Certain registries do not collect information on treatment pathways that are not disease-specific</td>
</tr>
<tr>
<td>Follow-up of patients during their entire treatment pathway</td>
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</table>
Conclusion

In summary, disease-specific data sources are available for certain diseases and provide solutions to data gaps in more administrative type datasets. Nevertheless, disease-specific data sources do have their own drawbacks (which vary depending on the source and the methodology used to collect data) and these must be borne in mind. Table 1 provides a summary of key advantages and disadvantages. These shortcomings include the fact that for some sources, the data represent a restricted study population – generalizable only for that specific group of patients. Further, information available is limited to what was collected, so data may not serve a wider range of research purposes. Finally there may not be an appropriate comparator group within the data (e.g., individuals without disease or with another disease).

Real-world data in its various forms – routinely collected or disease specific, longitudinal or cross-sectional, retrospective or prospective - have an important role to play in the evaluation of epidemiology and burden of disease, treatment patterns, compliance, persistence, and health outcomes of different treatments. Many study designs are possible but the limitations of each require careful consideration. A critical assessment of the available data sources to identify those that yield the best information for the study needs is essential. An informed decision must take into account several characteristics of the data source, including data content and data source accessibility.

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REFERENCES


In order to achieve successful market access, it is essential for medical device manufacturers to understand market dynamics, requirements, assessment criteria and most importantly, associated stakeholders.

However, in contrast to pharmaceutical market access where information, guidance and learned insights are often in the public domain, only seldom is public information or best practices available for medical devices. Additionally, market access requirements and processes for medical devices vary greatly from country to country. Examples are listed below.

**Classification varies by country.** In Brazil, medical devices are defined as Class I, II, III or IV, while in France, Italy and Germany medical devices are defined as Class I, IIa, IIb or III. Product types in each class include, for example:

- Class I: Stethoscopes, incision drapes, conductive gels
- Class IIa / II (Brazil): Cannula or insulin syringe, lancets, tracheal tubes
- Class IIb / III (Brazil): Intra-ocular lenses, surgical lasers
- Class II / IV (Brazil): Stents, pacemakers, defibrillators

**Health economic evidence** is valuable in all markets; however, cost savings are of highest importance in Brazil and increasingly across Italian regions, whereas cost effectiveness is of greatest importance in markets such as the United Kingdom (UK) and, increasingly, in France.

**Health technology assessment (HTA)** is a central, well-defined, formal process for medical devices in France and Germany, is regionalized across Italy with a few prominent regions having individual HTA bodies, and is still an emerging process in Brazil.

**Introduction of novel, high cost devices into the market varies greatly.** Germany, France and Italy have additional budgets and formal procedures, whereas Brazil does not have any specific procedures under the Sistema Único de Saúde (SUS), Brazil’s publicly funded healthcare system. Private systems are usually the early adopters of new technologies but often serve a smaller segment of the market catering to high income individuals. Private (out-of-pocket) healthcare - and therefore access to medical devices - is very common in Brazil; however, it is of moderate value across other markets. *(Note: discussion excludes specific targeting of Brazilian private market.)*

As a result of these country-specific intricacies, stakeholders and evidence requirements for medical device market access are difficult to identify. Medical device companies must carry out meticulous country-by-country analyses to obtain a thorough understanding of which evidence drives value and what requirements and processes must be met to launch a particular medical device. There is limited transferability of learning from one device launch to another due to rapidly changing evidence requirements, different classifications, and ever-growing stakeholder communities; this challenges product teams and leads to the collection of new, device-specific information for each launch.

**First step into the maze – understand the differences and their origins**

Planning for a medical device launch starts with understanding the most fundamental conditions of accessing a market, including procedures, stakeholders, and requirements. It is also essential to be aware of any recent or anticipated changes to the market access environment.

To allow efficient global launch planning for medical devices, markets can be clustered according to access conditions. All clusters assume technical controls and regulatory assessments as needed.
Cluster 1: Market success depends on strength and reach of marketing

Launch planning: Driven by marketing groundwork, including messaging, coalition with end-target users, and price sensitivity

Launch targets: Users (physicians or patients), purchasers (hospitals, physicians, nurses, wholesalers or/and pharmacists), and/or recipients (patients or family members of patients), depending on the device

Price: Defined by market demand, price of comparator products and discounts, available technology, and improvements in overall benefits

Coverage: Largely out of pocket or copayments

Requirements of manufacturer’s local team: Knowledge of demand, target size, messaging and sales force needs

Example markets: China, India, select markets in South America and the Middle East

Cluster 2: Market success depends on meeting pricing and reimbursement requirements and marketing

Launch planning: Needs to meet local reimbursement conditions (e.g., medical devices of a particular class can/cannot be reimbursed) and price assessment or maximum price fix; price and reimbursement opportunities are driven by marketing and similar marketing planning as in Cluster 1 applies

Launch targets: All of Cluster 1 audiences, plus government, semi-government, or private agencies that regulate reimbursement or price, often associated with purchasing

Price: Price must balance the affordability versus the innovation premium; generic devices need to consider the price of comparator products

Coverage: In some markets, all eligible medical devices are covered independent of class; in other markets, coverage is only for Class I-IIb devices; significant out-of-pocket or copayments

Requirements of manufacturer’s local team: Expertise in reimbursement, price negotiations, and local requirements. Knowledge of demand, target size, messaging, and sales force needs

Example markets: Russia, Brazil, select Central Eastern European markets

Cluster 3: Market success depends on demonstrating value

Launch planning: Needs to be based on providing scientific evidence which demonstrates the value of the medical device to patients, caregivers, and the health system (or innovation in some markets); requires knowledge on what type of evidence is recognized in different markets as valid for value demonstration; penetration of the market requires detailed marketing planning as in Clusters 1 and 2

Launch targets: All of Cluster 1 audiences, plus government, semi-government or private agencies that conduct value assessments; important launch targets are national, regional, or budget holders and purchasing groups

Price: Pricing depends on level of demonstrated value (level of innovation in some markets), comparator products price, and either mandatory or negotiated discounts

Coverage: Depends on co-pay regulations per market and prescription requirements (e.g., copayments are more common across France and Italy than in Germany, especially true for devices of Class I to IIa

Requirements of manufacturer’s local team: Expertise in scientific and health economic value demonstration, knowledge of reimbursement and price negotiations and local requirements; knowledge of demand, target size, messaging, sales force needs, purchasing requirements, and fund holding

Example markets: European Union (EU), United States (U.S.), Canada and Australia

The prescriptiveness of clusters and the factor of time

The use of clusters allows for recognition of the basic information and formulation of a plan, including anticipated timing of execution and planning of resources. It is important to obtain this information early in the planning phase in order to calculate the benefits/risks of different routes and allow for any missing information to be obtained.

However, country access systems for medical devices develop fast. The natural progression is for markets to transition from Cluster 1 to Cluster 2 and 3, while markets rarely shift in the opposite direction. Therefore, over time, markets are likely to increase their demands, requirements for access, and number of stakeholders involved. As a result, more health technology skills in medical device companies are required. Clustering allows the monitoring of requirements by market attributes and can help to anticipate future changes to requirements, although country-specific differences should also be considered.

Limitations of clustering and transparency

Most of the critical requirements for medical device market access planning for Clusters 2 and 3 are not well
published or promoted by the relevant organizations. This contrasts to the pharmaceutical access pathways, where processes, timelines, data requirements, and evidence needs are well communicated and stakeholders are generally easier to identify.

Therefore, clustering is only a first step in creating transparency. Appropriate launch planning requires additional details to allow for a full assessment of preparation needs, investment, risks, and benefits. The critical differences between markets that were described earlier often only transpire when individual markets are investigated in depth.

**Start with the End in Mind**

To allow for launch opportunity assessment, an early comparative definition of value and opportunity needs to be conducted as outlined below.

1. A **value repository** adapted to the device class and market requirements
   - Technical profile of the device and its value proposition, as well as identification of competitors and their value propositions
   - Summary of market access environment, including: a) Current funding and coding; b) Expected changes and challenges; and c) Price of current products (if applicable)
   - Map assessment process in a specific market and associated timelines

2. **Stakeholder mapping** identifying level of relevance and importance for the market access of the device (adapted to the device)
   - Consider stakeholders: Market access assessment, budget decision makers, purchasers, and users

3. An **environment compendium** allowing for the assessment of risks and identification of ways to manage risks. Components of the compendium should be adapted to the device, and include the following basic parameters - across device classes – to be investigated for a) timelines; b) processes; and c) strategic imperatives:
   - Purchasing and distribution pathways
   - Funding and budget holding
   - Pricing, copays, and discounting
   - National/regional renegotiation of price

4. **Prospective influences** that potentially offset additional planning imperatives, adapted to the device (the list below is non-exhaustive):
   - Per SWOT (strengths, weaknesses, opportunities, threats) assessment, identify the stakeholder action points needed to ensure that the market access process is well supported and accompanied by the appropriate communication of evidence for each audience
   - External business environment: competitor developments and their potential positioning and request for funding; changes in copayments or fees for service/use; new stakeholders and evidence requirements; new pathways to integrate medical devices in health service delivery (including push for homecare)
   - Internal business capability: organization of responses to address new evidence needs

Table 1 highlights selected country-specific market access information that is important for launch opportunity planning and market access preparation of a device in Cluster 2 and 3 markets.
Table 1: Cross-Country Comparison of the Key Elements of Market Access for Medical Devices Based on Information Obtained in 2014 and 2015

<table>
<thead>
<tr>
<th>Context</th>
<th>FRANCE</th>
<th>GERMANY</th>
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<th>BRAZIL</th>
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<tr>
<td>Health system</td>
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<tr>
<td>• More than 70% expenditure on medical devices comes from public health system in the EU</td>
<td>National social insurance</td>
<td>Statutory health insurance (Approx. 77% of healthcare spending is sourced from the public sector)</td>
<td>Tax funded healthcare system. More than 75% of device expenditure covered by public healthcare system</td>
<td>Statutory health insurance provided to all (150 million patients), a third of which (50 million patients) also pay for private health insurance</td>
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<td>• Variations in Brazil</td>
<td>Over 90% population covered under compulsory, additional, complimentary health insurance called mutuelles</td>
<td>Small percentage covered under private health insurance or competitive governmental schemes (only approx. 20%)</td>
<td>The role of private health insurance is very limited; in 2009, it accounted for only 1% of total health spending</td>
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<td>Hospital payment system</td>
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<td>• Heavy investments on medical devices are concentrated in the hospitals</td>
<td>GHS (Diagnosis Related Groups [DRG])</td>
<td>G-DRG</td>
<td>DRGs are nation-wide; however, regions can adapt tariffs and codes to some extent</td>
<td>Public sector: Capital budget-national budget distributed amongst regional/municipal bodies</td>
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<td>• Rather than routine HTA processes, additional routes are available for early access of innovative devices</td>
<td>PSTIC (Programme de soutien aux technologies innovantes, coûtées ou non)</td>
<td>NUB (for devices not included in G-DRG; hospital specific)</td>
<td>Additional payments for high-cost, innovative devices are regionally controlled; when regions publish the updated DRG lists, there is a section which specifies the devices/procedures for which an additional payment can be claimed.</td>
<td>No specific mechanisms available to support innovative high-cost devices</td>
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<tr>
<td>Classification system</td>
<td>Devices are classified from a regulatory level into different grades based on level of risk and invasiveness</td>
<td>CE mark (Class I, IIa, IIb, III)</td>
<td>CE mark (Class I, IIa, IIb, III)</td>
<td>ANVISA (Brazilian health Surveillance Agency) registration (Class I, II, III, IV)</td>
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<td>Process of assessment for low risk devices (Classes I-II)</td>
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<tr>
<td>• Not all devices are assessed by HTA bodies; generic and low-risk devices pass through simpler routes</td>
<td>Class I devices</td>
<td>Not assessed by GBA (Der Gemeinsame Bundesausschuss) if new product has low innovation value (class independent) or if generic medical device/implant – straight to SHI (statutory health insurance) for assessment</td>
<td>Low-risk devices likely to be assessed by CPTOs (Commissione Prontuario Terapeutico Osipedalierno)</td>
<td>Public sector: CONITEC (Comissao Nacional de Incorporaçao de Tecnologias) does not assess lower risk devices (i.e. Class II); however, some higher risk/more novel Class III devices may still be subject to assessment</td>
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<tr>
<td>Process of assessment for high risk devices (Classes II-III for EU and II-IV for Brazil)</td>
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<tr>
<td>• Devices are assessed by various HTA bodies only under given circumstances</td>
<td>Conducted in the following cases (mainly Class II-III): A)</td>
<td>If new product has high innovation value or there has been a lack of prior assessments of similar products in the past (mainly Class II-III)</td>
<td>No national level HTA body exists, national bodies have a role of consulting/supervising regional bodies</td>
<td>Public sector: Higher risk devices (primarily Classes III and IV) are assessed by CONITEC</td>
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<tr>
<td><strong>Assessment bodies (HTA)</strong></td>
<td>• Different bodies are involved in HTA assessment process of the devices</td>
<td>• HAS (Haute Autorité de santé)</td>
<td>• IQWIG (Instituts für Qualität und Wirtschaftlichkeit im Gesundheitswesen)</td>
<td>• Public: CONITEC</td>
</tr>
<tr>
<td></td>
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<td>• Clinical and technical evaluation body (CNEDIMTS)</td>
<td>• GBA</td>
<td>• Private: HMOs</td>
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<td>• Economic evaluation: CEPS and CEEPS (La Commission évaluation économique et de santé publique)</td>
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<tr>
<td><strong>Data requirements</strong></td>
<td>• Data requirements are not that transparent for medical devices as they are for pharmaceuticals</td>
<td>• Technical description of technology</td>
<td>• Lack of specific guidance</td>
<td>• Public (CONITEC): Technical, clinical, economic data; QoL data also considered; no QALY limits but there are standards and some HE evidence is expected</td>
</tr>
<tr>
<td></td>
<td>• Very basic guidance is provided by HTA bodies</td>
<td>• Specification of use</td>
<td>• follows directive of pharmaceutical products</td>
<td>• Private: pharmacoeconomic data but less robust and rigid process; should also provide technical and clinical data also</td>
</tr>
<tr>
<td><strong>Length of assessment</strong></td>
<td>• Assessment period varies across different countries and sometimes may be much longer than given in the guidance</td>
<td>• Approx. 1 to 1.5 years for new devices/new GHM</td>
<td>• Approx. 3 to 6 months if assessed by SHI only/G-DRG code exists</td>
<td>• Public: 6 to 9 months</td>
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<td>• Approx. 6 months, if already exists in a GHM</td>
<td>• 1.5 to 3 years GBA/IQWIG</td>
<td>• Private: as little as 2 months</td>
</tr>
<tr>
<td><strong>Final decision</strong></td>
<td>• Final assessment decision may be made at the national/regional level</td>
<td>• Ministry of Health (MoH)/HAS are the final decision-makers</td>
<td>• GBA responsible for final decision</td>
<td>• Public: MoH/SUS</td>
</tr>
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<td>• Decision published in Official Journal of the French Republic</td>
<td>• Decision not officially published, manufacturer can decide to publish the outcome</td>
<td>• MoH has 180 days to publish a final reimbursement deliberation in the Official Gazette from the request date, which can be extended by up to 90 days</td>
</tr>
<tr>
<td><strong>Budget holders</strong></td>
<td>• Budget holders are responsible for final uptake of medical devices in hospitals</td>
<td>• Members of COMEDIMS</td>
<td>• Regional budget holders</td>
<td>• Public: Government; Ministry of Health will decide who should pay for the device</td>
</tr>
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<td>• Members of mutuelles</td>
<td>• Local health units</td>
<td>• E.g., very expensive novel technologies may be funded from the national budget, while all others will be funded by the State or Municipality budgets</td>
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<td>• Head of relevant department at university hospitals</td>
<td>• Head of relevant department at hospitals</td>
<td>• Private: HMOs and private hospitals</td>
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<td></td>
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<td>• Members of purchasing groups</td>
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**THE EVIDENCE FORUM**
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<tr>
<th><strong>Context</strong></th>
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<tr>
<td><strong>Pricing (inpatient devices only)</strong></td>
<td>Pricing covered by various bodies can be split into ambulatory and hospital sector</td>
<td>CEPS and CEEPS allocate a national price for products on LPPR (Liste des produits et prestations remboursables)</td>
<td>GKV[^4]</td>
<td>Government (MoH, states, municipalities depending on who pays for it)[^4]</td>
</tr>
<tr>
<td><strong>Early scientific advice</strong></td>
<td>Similar to pharmaceutical sector, seeking early scientific advice is considered beneficial in countries where the possibility exists</td>
<td>Available</td>
<td>Available</td>
<td>Not available</td>
</tr>
<tr>
<td><strong>Stakeholders</strong></td>
<td>Highly influential stakeholders in decision making (i.e., scored 5 and 4)[^3]</td>
<td>National/regional procurement groups</td>
<td>National/regional procurement groups, alliance between manufacturer and budget holders, SHI</td>
<td>Public: HTA (CONITEC), government departments (SUS, States, municipalities)</td>
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<td>National and regional budget holders, MoH (DGS and DSS), ambulatory physicians, nurses, policy makers</td>
<td>MoH (DGS and DSS), IQWiG, manufacturer*, national and regional budget holders, policy makers</td>
<td>Private; HMOs and hospitals</td>
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<td>Medical societies and physicians – main players (company works behind the scenes), HTA bodies (only in regions where these exist), university hospitals (best relationships with agencies), regional budget holders (very important)</td>
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<td>Physicians in hospital, ambulatory physicians, patients, nurses, and health economists</td>
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<td>Pharmacists</td>
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<td>Purchasing groups or national/regional procurement</td>
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</table>
**The manufacturer can contact the SHI (usually via consulting agencies) at the very beginning of the process to inform them of the upcoming submission and try to make them curious. This might lead to collaboration between the manufacturer and the budget holders with the aim to save costs and speed up the process (e.g., manufacturer can get consultation and even help with planning and conducting the trials). An alliance between the manufacturer and budget holder is very influential.**

**Pricing processes for ambulatory devices were not discussed specifically with interviewees.**

<table>
<thead>
<tr>
<th>Challenges</th>
<th>France</th>
<th>Germany</th>
<th>Italy</th>
<th>Brazil</th>
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</thead>
<tbody>
<tr>
<td>Challenges of the current procedures for the device manufacturers*</td>
<td>Assessment of combination of medical devices and drugs</td>
<td>A very complex system; no transparency; administrative barriers, mistakes in filing can lead to considerable delays</td>
<td>Limited economic resources (even more so than rest of Europe)</td>
<td>Production of robust clinical and economic evidence; a good economic analysis needs local data whereas clinical data does not need to be local and foreign studies in reliable centers anywhere in the world are acceptable.</td>
</tr>
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<td></td>
<td>Lack of registries and outcomes data for comparison</td>
<td>Linking the benefits as provided by the manufacturer to real-world evidence</td>
<td>Regional variability</td>
<td>Pharmacoeconomic evaluation is very new in Brazil so local data is scarce.</td>
</tr>
<tr>
<td></td>
<td>Lack of pricing information across EU</td>
<td>Lack of review of generic lines of devices</td>
<td>Almost best if you have competitors already in market so the pathway already exists and is a lot more straightforward than obtaining novel code</td>
<td>Public health system is very ambitious; budget constraints are very important.</td>
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<tr>
<td>Trends</td>
<td>CNEDIMTs - a strong member of the European Network for Health Technology Assessment (EUnetHTA), shaping early dialogues</td>
<td>No major changes expected in HTA processes in the foreseeable future.</td>
<td>Increasingly frequent grouping of hospitals which results in greater procurement power and control</td>
<td>Private segment will grow substantially – the population obtaining private insurance is growing, and with this the level of investment and access to new technologies will also increase</td>
</tr>
<tr>
<td></td>
<td>Broadening the definition of combined drugs</td>
<td>HTA procedures and requirements are expected to get even stricter in the future. The additional benefit offered by the new device will be questioned in more depth, making it more difficult to get reimbursement for me-too devices that are more expensive than the standard of care.</td>
<td></td>
<td>CONITEC will introduce more medical devices for coverage; however, they will likely train medical societies and nurses to develop a network which will contribute to the decision-making process</td>
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<tr>
<td></td>
<td>Increase in home care devices as elderly patients seek greater autonomy</td>
<td>However, innovation will remain of paramount importance</td>
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<td>Continued investment in local production; incentives for Brazilian companies to produce locally</td>
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<td>Robustness of technology evaluation will increase in private sector</td>
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<td>Increased patient power/ importance of patient organizations</td>
</tr>
</tbody>
</table>

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*The manufacturer can contact the SHI (usually via consulting agencies) at the very beginning of the process to inform them of the upcoming submission and try to make them curious. This might lead to collaboration between the manufacturer and the budget holders with the aim to save costs and speed up the process (e.g., manufacturer can get consultation and even help with planning and conducting the trials). An alliance between the manufacturer and budget holder is very influential.

**Pricing processes for ambulatory devices were not discussed specifically with interviewees.**
How to arrive on the other side of the maze:
recommendations

• Know the access systems and decision makers for medical devices well

• Define your key strategic value substantiation objectives at product investigation stage to meet HTA requirements or marketing needs

• Start planning early for stakeholder engagement for marketing and HTA activities, and use the support of early advice where appropriate

• Focus on the end user, while not losing sight of the buyer

• Value proposition is a function of having a clear understanding per market on how to meet requirements, communicating the need, and creating a win-win situation for both buyer and seller

For more information, please contact Laura.Haycock@evidera.com, or Helena.Emich@evidera.com.

REFERENCES


4 Information Collected from a Total of 6-8 Payer Interviews done by Evidera; 1-2 in Brazil, 2-3 in France, 2-3 in Germany and 1-2 Italy.


Addressing Unique Challenges Faced by Small to Medium Biopharma in Value Demonstration

L. Clark Paramore, MSPH, Vice President, Value and Evidence Planning, Evidera

In recent years there has been a noticeable increase in the participation of small- to medium-sized biopharmaceutical companies in the development of new therapies. According to one recent analysis, these companies increased their share of innovation origin (based on the number of new molecular entities) from 50% in 2004 to 73% in 2014. Statistics from the European Medicines Agency (EMA) indicate that 27% of new drugs introduced in the European market from 2010 to 2012 were from small to medium biopharma. There has been a corresponding increase in the proportion of small to medium biopharma companies deciding to commercialize products themselves. This is due in part to the highly specialized nature of many therapies (e.g., orphan drugs) that may require a smaller scale as related to sales and marketing investment. As these companies move towards commercialization, they face unique challenges in meeting today’s increasingly demanding evidentiary requirements and demonstrating the value of their new therapies. In this article, we describe these challenges - considering the business model that underlies them - and then summarize how Evidera engages with small to medium biopharma to address the challenges.

Value Demonstration Challenges for Small to Medium Biopharma

Small to medium biopharma companies face a business environment that is similar to that of most start-up companies: dependence on a single or very limited number of pipeline products, limited funding and the ongoing search to find additional investors, and pressure from investors to show a quick and high return on their investment. Given this environment, many of these companies (especially small biopharma) have made a strategic decision to be lean and nimble, hiring a limited staff that possess mainly scientific or entrepreneurial expertise.

As shown in Figure 1, the strategic decision by these companies to maintain a lean and efficient organizational structure leads to specific challenges vis-à-vis health economics and outcomes research (HEOR)/market access activities. One set of challenges relate to **resource optimization**. Typically there may be just one or two individuals within the company who are responsible for HEOR and/or market access, and often these individuals have very limited exposure to the needs in this space. As a result, they need to look outside their organization to obtain the necessary expertise. This expertise needs to cover a broad set of methods and approaches, and ideally address geographic variation. Given the individual(s)' responsibilities and workload, it is critical to identify an external partner who has the breadth and depth of HEOR/ market access expertise. The HEOR/market access lead also faces a situation where the ‘share of voice’ is small relative to other functions within the organization.
Thus there are typically limited budgets for non-trial-related evidence generation (e.g., real-world studies) that may be important for market access considerations.

Small to medium biopharma companies also face key challenges in obtaining and maintaining an adequate knowledge base of the market landscape relevant to their product(s). There is constant change in the level of influence of the various stakeholders (e.g., providers, payers, patients) who will make decisions on the use and uptake of their product(s). Health technology assessment is becoming more formalized and increasingly complex, with significant variation in the processes being chosen by agencies in various countries. Due to the highly specialized nature of many new products in development, there is a dearth of information on the disease burden of the niche target populations – and this information will be critical for decision makers to understand the value proposition of these therapies.

A third set of challenges relates to the generation of the necessary evidence to demonstrate product value. Limited budgets mean that not every good HEOR study idea will be funded. There are some studies that will be viewed as necessary and others as ‘nice to haves’ – thus the rationale and justification for study prioritization are critical for small to medium biopharma executives who will have to make the case to their investors. The overall program of HEOR/market access activities will need to be designed in a thoughtful and integrated manner to ensure efficiencies and optimization of the available budget. And finally, studies that are funded will need to produce results in a timely manner to support critical go/no-go decisions and help justify additional funding from investors.

Addressing the Challenges with Early Commercialization Support

Figure 2 presents a suggested approach for providing small to medium size biopharma companies optimal early commercialization support that addresses the challenges just described. First, a partner such as Evidera, which has the broad expertise necessary to address the various questions included in each step of the process, offers the HEOR/market access lead a cost-effective outsourcing option. Second, Steps 1-3 in Figure 2 provide answers to some of the key knowledge management issues including 1) a detailed understanding of disease burden for the relevant target patient population, 2) in-depth perspectives from stakeholders on key value attributes, and 3) what evidence will regulators and payers need and expect to receive. Finally, a strong evidence generation strategy will result in a well-designed and cost-effective study plan. This will produce the right evidence for value demonstration that will ultimately get to the right audience at the right time.

For more information, please contact Clark.Paramore@evidera.com.

REFERENCES


2016 – The Year to Focus Real-World Evidence on Pricing and Reimbursement

EVIDERA’S PRICING AND REIMBURSEMENT POLICY COUNCIL (PRPC) provided feedback in September 2015 on key topics. A short synopsis is highlighted below.

(Membership of the PRPC include: National Payers and Advisers to Pricing and Reimbursement Committees in England, Germany, France, Italy and Spain – one member per market.)

### 1. Indications of importance for Real-World Evidence Generation to inform pricing and reimbursement of new molecules

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<tr>
<th>Country</th>
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<th>3rd</th>
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<tbody>
<tr>
<td>Italy</td>
<td>Orphan indications</td>
<td>Cancer and Autoimmune Conditions (Rheumatoid Arthritis [RA], Crohn’s Disease, Psoriasis)</td>
<td>Cancer and Autoimmune conditions (RA, Crohn’s Disease, Psoriasis)</td>
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<tr>
<td>Spain</td>
<td>Cancer</td>
<td>Diabetes, Dyslipidaemia</td>
<td>Autoimmune Conditions (RA, Crohn’s Disease, Psoriasis)</td>
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<tr>
<td>Germany</td>
<td>Diabetes</td>
<td>Dyslipidaemia</td>
<td>Dementia</td>
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<tr>
<td>France</td>
<td>Diabetes</td>
<td>Autoimmune Conditions (RA, Crohn’s Disease, Psoriasis)</td>
<td>Selected Cancers</td>
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<td>England</td>
<td>Cancer</td>
<td>Cardiology</td>
<td>Respiratory</td>
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### 2. Should the evidence be provided pre-launch or post-launch?

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<th>Country</th>
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<td>Cardiology</td>
<td>Respiratory</td>
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### 3. For market access decision-making in your country, will price increase in importance compared to all other pricing and reimbursement requirements?

<table>
<thead>
<tr>
<th>Country</th>
<th>Answer</th>
<th>Verbatim Comments</th>
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<tbody>
<tr>
<td>Italy</td>
<td>Yes</td>
<td>‘Pricing per indication may represent a possible evolution’</td>
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<tr>
<td>Spain</td>
<td>No</td>
<td>‘Health economics is more meaningful than price!’</td>
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<tr>
<td>Germany</td>
<td>Yes</td>
<td>‘Health economics is not an issue for us – but obviously price is!’</td>
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<tr>
<td>France</td>
<td>No</td>
<td>‘For us, the next step will be to complement economic evaluation (efficiency) with budget impact models (affordability). That is, something more complex than simple price.’</td>
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<tr>
<td>England</td>
<td>Yes</td>
<td>‘To some extent, affordability will bite harder! [There is] potential for more competitive tendering to drive price down in areas where several products have [the] same efficacy.’</td>
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For more information, please contact Susanne.Michel@evidera.com.
PLENARY SESSION

Wed., 11 Nov, 11:15 - 12:30
Presentation of the Task Force Reports: Emerging Good Practices for Conducting MCDA
Moderator: Malone D
Speakers: Ljerman MJ, Marsh K

Session V – Wed., 11 Nov, 13:45 – 14:45
W25: Incorporating Equity into Health Technology Assessment: An Illustration and Critical Review of Good Practice
Discussion Leaders: Marsh K, Omelyanovskiy VV, Morton A, Sri Bhasthym S

Session VI – Wed., 11 Nov, 15:00 – 16:00
W33: Uncertainty of Uncertainty Estimates in EconomicModelling of Oncology
Discussion Leaders: Lanitis T, Kalo Z, Muszbek N

SHORT COURSES

Sun., 9 Nov, 8:00 - 12:00
Discrete Event Simulation for Economic Analyses – Concepts
Instructors: Caro JJ, Moller J

W4: Making Sense of Novel Approaches for Indirect Comparison: Similarities and Differences of Simulation and Matching Based Approaches
Discussion Leaders: Ishak KJ, Phatak H, Masseria C

Sun., 8 Nov, 13:00 - 17:00
Discrete Event Simulation for Economic Analyses – Applications
Instructors: Caro JJ, Moller J

Sun., 8 Nov, 13:00 - 17:00
Using Multi-Criteria Decision Analysis in Health Care Decision Making: Approaches & Applications
Instructors: Ljerman M, Marsh K, Devlin N, Praveen Thokala P

WORKSHOPS

Session I – Mon., 9 Nov, 17:00 - 18:00
W4: Making Sense of Novel Approaches for Indirect Comparison: Similarities and Differences of Simulation and Matching Based Approaches
Discussion Leaders: Ishak KJ, Phatak H, Masseria C

Session II – Tues., 10 Nov, 8:45 – 9:45
W10: Moving the Science Forward: Tackling Key Psychometric and Methodological Issues Facing the Field of Clinical Outcomes Assessment
Discussion Leaders: Symonds T, Wyryich KW, Regnault A, Coons SJ

POSTERS

Session I – Mon., 9 Nov, 8:45 - 14:15
PCV134: A Systematic Review of Cardiovascular Event Utilities in Europe
Bleden M, Smith D, Becker BT, Paoli CJ, Gandra SR

Session II – Mon., 9 Nov, 11:15 - 12:15
IP3: Speed or Less Uncertainty? Trade-offs in Adaptive Pathway Implementation and Potential Pricing and Reimbursement Responses
Moderator: Michel S
Panelists: Boehler YB, Buxton M, Caro JJ

SESSION PANEL

Session I – Mon., 9 Nov, 11:45 - 12:45
Discussion Leaders: Lanitis T, Kalo Z, Muszbek N

PCV13: Cost-Effectiveness of Apixaban Compared to Low Molecular Weight Heparin/ Edoxaban for Treatment and Prevention of Recurrent Venous Thromboembolism
Lanitis T, Hamilton M, Quon P, Browne C, Masseria C, Cohen A

PCV123: Cost-Utility Analysis of Apixaban in the Acute Treatment and Prevention of Venous Thromboembolism in France
Stern S, Cotte FE, Minacori R, Gosden T, Hamilton M, Phatak H, Quon P

PCV32: Demographics, Clinical Characteristics, and Treatment Patterns of Patients Newly Started on Prostacyclin Therapy for Pulmonary Arterial Hypertension

PCV7: Systematic Literature Review of the Burden of Illness in Hypertriglyceridemia
Martin AL, Travers K, Burns M, Palmer M, Henriksson KM, Rikner K

SESSION II – Mon., 9 Nov, 15:45 - 19:45

PCN214: Estimating EORTC-8D Health State Utility Values from EORTC QLQ-C30 Scores in Relapsed Multiple Myeloma
Ashaye AO, Altincatal A, Bender RH, Zhang J, Panjabi S

PCN234: A Systematic Review of Cardiovascular Event Utilities in Europe
Bleden M, Smith D, Becker BT, Paoli CJ, Gandra SR

Session III – Mon., 9 Nov, 17:00 - 18:00

Conference Chair: Dubois A

PCV12: Cost-Utility Analysis of Apixaban in the Acute Treatment and Prevention of Venous Thromboembolism in France
Stern S, Cotte FE, Minacori R, Gosden T, Hamilton M, Phatak H, Quon P

PCV32: Demographics, Clinical Characteristics, and Treatment Patterns of Patients Newly Started on Prostacyclin Therapy for Pulmonary Arterial Hypertension

PCV7: Systematic Literature Review of the Burden of Illness in Hypertriglyceridemia
Martin AL, Travers K, Burns M, Palmer M, Henriksson KM, Rikner K

PCV71: Resource Utilisation and Costs in Patients with Post-Stroke Spasticity in the United Kingdom
Raluy-Callado M, Cox A, MacLachlan S, Gabriel S, Dinet J

PCV121: Integrating Health State Utilities in a Health Economic Modelling Framework for Pulmonary Arterial Hypertension
Polonsky WH, Kerr D

PCV75: Health State Utilities Associated with Attributes of Weekly Injection Devices for Treatment of Type 2 Diabetes
Matza LS, Stewart KD, Davies E, Paczkowski R, Boye KS

PCV129: Health State Utilities Associated with Glucose Monitoring Devices
Matza LS, Stewart KD, Davies EW, Hellmund R, Polonsky WH, Kerr D

PCV35: Patterns of Utilization and Cost of Prostacyclins for Pulmonary Arterial Hypertension

PCV71: Resource Utilisation and Costs in Patients with Post-Stroke Spasticity in the United Kingdom
Raluy-Callado M, Cox A, MacLachlan S, Gabriel S, Dinet J

PCV7: Systematic Literature Review of the Burden of Illness in Hypertriglyceridemia
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PCV71: Resource Utilisation and Costs in Patients with Post-Stroke Spasticity in the United Kingdom
Raluy-Callado M, Cox A, MacLachlan S, Gabriel S, Dinet J
Session III – Tues., 10 Nov, 8:45 - 13:45

PIN27: Challenges in Economic Evaluation of Antibiotics in Health-Care Acquired Infections: A Targeted Review
Chapman R, Kongnakorn T

PIN84: Health State Utilities of Risks Associated with Antiretroviral Treatment for Human Immunodeficiency Virus (HIV)

Session IV – Tues., 10 Nov, 15:15 - 19:15

PDB93: Evaluating Diabetes Patients’ Preferences for Profiles of GLP-1 Treatments in the United Kingdom: A Discrete Choice Experiment
Gelhorn HL, Poon JL, Davies EW, Paczkowski R, Curtis SE, Boye KS

PSY80: Health State Utilities for Gaucher Disease Type 1

PSY77: Retrospective Cohort Study Using Data from the UK Clinical Practice Research Datalink and Hospital Episode Statistics to Assess Unplanned Hospitalisation in Patients with Multiple Myeloma
Ralyu-Callado M, Lambrelli D, DeCosta L, Gonzalez-McQuire S

Session V – Wed., 11 Nov, 8:45 - 13:45

PND53: Abobotulinumtoxin A in the Management of Cervical Dystonia in the United Kingdom: A Cost-Effectiveness Analysis
Desai K, Muthukumar M, Abogunrin S, Harower T, Dinett J, Gabriel S

PRM177: Assessment of Content Equivalence and Usability between the Paper and Electronic Versions of the Psoriasis Symptom and Sign Diary (PSSD) among Subjects with Plaque Psoriasis
Eremenco S, McQuarrie K, Brooks A, Landrian A, Maguire S, Shepherd P, Han C

PND45: Cost-Effectiveness Analysis of Peginterferon Beta-1A in the Treatment of Relapsing-Remitting Multiple Sclerosis in Ireland
Hernandez L, Guo S, Toro-Diaz H, Carroll S, Syed Farooq SF

PND43: Cost-Effectiveness Analysis of Peginterferon Beta-1A in the Treatment of Relapsing-Remitting Multiple Sclerosis in Scotland
Hernandez L, Guo S, Toro-Diaz H, Carroll S, Syed Farooq SF

PRM197: Development of a Measure to Assess Severity of MPS II: The Disease Severity Score
Vernon MK, Ralyu-Callado M, Trundell D, Wklund I, Pullis T, Whitman DAH

PRM101: Implementation of Population Dynamics in Modelling Health and Budget Impact of an Intervention for a Chronic Disease with Multiple Disease Subtypes
Tran-Duy A, Boonen A, Caro JJ, Severens JL

PRM235: Let’s Talk! Is Chatter on Social Media Amongst Participants Compromising Clinical Trials?
Merinopoulou E, Chalkiadaki C, Abogunrin S, Lambrelli D, Cox A

PRM19: Machine Learning for Identifying Potentially Undiagnosed Post-Stroke Spasticity Patients in United Kingdom
Cox A, Ralyu-Callado M, Wang M, Bakheit A, Moor P, Dinett J

PRM195: Migration of the Fatigue Symptoms and Impacts Questionnaire-Relapsing Multiple Sclerosis (FSIQ-RMS) from Paper to an Electronic Diary Format
Eremenco S, Shaffer S, Schuler R

PRM100: Modeling the Natural History of Secondary-Progressive Multiple Sclerosis: A New Modeling Approach Using Discrete Event Simulation
Hernandez L, Guo S, Altcinatal A, Naoshy S, Watson C

PRM94: Modeling Treatment Sequences in Health Technology Assessments
Zheng Y, Pan F, Sorensen S

PRM277: Moving Beyond the PICOS: Appropriate Comparative Observational Data Selection Can Facilitate Meta-Analysis of Relative Treatment Effects
Sallum R, Zhang Y, Xu Y

PRM162: Qualitative Equivalence between Paper and eDiary Versions and Usability of 4 PRO Questionnaires for Uterine Fibroids
Eremenco S, Stringer S, Gleeson S, Landrian A, Falcon I

PRM192: Qualitative Equivalence between Paper and eDiary Versions and Usability of 6 PRO Questionnaires for Endometriosis
Eremenco S, Stringer S, Gleeson S, Landrian A, Falcon I

PRM137: Scoring and Responsiveness of the Self-Assessment of Treatment Version II Questionnaire in Patients with Painful Diabetic Peripheral Neuropathy
van Nooten F, Trundell D, Staniewska D, Revicki DA

PRM208: Simulated Treatment Comparison of Time-To-Event (and other Non-Linear) Outcomes
Ishak KJ, Rael M, Phatak H, Masseria C, Lanitis T

PRM168: Survey of Neurologist’s Current Practices in Evaluation of Multiple Sclerosis to Identify Domains for a New Clinician-Reported Measure
Phillips GA, Matza LS, Stewart KD, Coyne K, Malley K

PRM44: The Economic Impact of Shape Formula for the Children of Overweight and Obese Mothers
Marsh K, Moller J, Basarir H, Detzel P
Upcoming Presentations

**AMCP Nexus 2015**
Oct 26-29, 2015; Orlando, FL, USA

**POSTERS**
Adherence to Quality Standards for Time to Initiation of Disease-modifying Anti-Rheumatic Drugs among Newly Diagnosed Rheumatoid Arthritis Patients
Bhurke S, Mohanty M, Bapat B, Bhagnani T, Tang DH, Shah N, Harrison DJ, Stolshek BS

Incident Events Associated with Use of Prostacyclins for Pulmonary Arterial Hypertension

**AHA Scientific Sessions 2015**
Nov 7-11, 2015; Orlando, FL, USA

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

**ASCP 2015**
Oct 30-Nov 1, 2015; Las Vegas, NV, USA

**POSTER**
Medication Adherence to and Treatment Patterns of Linagliptin and Sulfonylureas When Used as Second-Line after Metformin in Patients with Type-2 Diabetes Mellitus (T2DM)

**AASLD The Liver Meeting 2015**
Nov 13-17, 2015; San Francisco, CA, USA

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

**IPECAD 2015**
Nov 19-20, 2015; Boston, MA, USA

**ORAL PRESENTATION**
An ACE for Alzheimer's Disease: State of the Art Modeling
Caro JJ

**XXI World Congress on Parkinson’s Disease and Related Disorders**
Dec 6-9, 2015; Milan, Italy

**ORAL PRESENTATION**
Determination of Minimal Important Difference Thresholds for Parkinson’s Disease Questionnaire-39 in Advanced Parkinson’s Disease Patients
Antonini A, Bacci ED, Sail K, Jalundhwala YJ, Kandukuri PL, Marshall T, Chatamra K, Wiklund I, Revicki D

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**Predictors of Treatment Adherence and Discontinuation in Department of Defense (DoD) Health Care Beneficiaries Treated for Chronic Hepatitis C 2004-2013**
Teltsch D, Walker DR, Nordstrom B, Fraeman K, Kronmann K, St. Clair KJ

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**MISSED ANY OF OUR RECENT WEBINARS?**

View a complete listing of past webinars and ‘on demand’ options by visiting evidera.com.

- Indirect Treatment Comparison without Network Meta-Analysis: An Overview of Simulated Treatment Comparison (STC) and Matching Adjusted Indirect Comparison (MAIC)
- Statistical Methods for Demonstrating Endpoint Non-Redundancy among Clinical Trial Endpoints
- Real-World Database Analytics: Is a Sea Change Coming Soon?
- Predicting Alzheimer’s Disease Progression Using Archimedes Condition Event (ACE) Simulation
Recent Presentations

CHEST 2015
Oct 24-28, 2015; Montreal, Canada

POSTERS

Can Peak Flow (PEF) Aid in the Identification of Undiagnosed Clinically-Significant COPD?
Mannino D, Martinez F, Leidy NK, Bacci ED, Barr RG, Bowler RP, Han MK, Houfek JF, Make B, Malley KG, Meldrum CA, Rennard S, Thomashow B, Walsh J, Yawn BP

Identifying Patients with Undiagnosed Clinically-Significant COPD in Primary Care: What Questions Should We Be Asking?
Martinez F, Mannino D, Leidy NK, Bacci ED, Bowler RP, Han MK, Houfek JF, Make B, Malley KG, Meldrum CA, Rennard S, Thomashow B, Walsh J, Yawn BP

ISOQOL 22nd Annual Conference – 2015
Oct 21-24, 2015; Vancouver, Canada

WORKSHOP

An Introduction to Health-Related Quality of Life Assessment
Gelhorn H, Wywich K

POSTERS

A Community Sample’s Perception of Cause-and-Effect Directionality among Health Domains

Challenges and Opportunities for PROs and Big Data: Applications for the Pharmaceutical Industry
Lenderking WR

Development of the PROMIS Nociceptive Pain Scale
Nowinski C, Cella D, Revicki D, Amtmann D, Michaud K, Kallen MA, Askew RL

15th European AIDS Conference – 2015
Oct 21-24, 2015; Barcelona, Spain

POSTER

Health State Utilities of Risks Associated with Antiretroviral Treatment for Human Immunodeficiency Virus (HIV)
Matza LS, Chung KC, Kim KJ, Paulus TM, Davies EW, Stewart KD, McComsey GA, Fordyce MW

SMDM 2015
Oct 18-21, 2015; St. Louis, MO, USA

POSTER

Selection of Key PROMIS Domains for a Preference-Based Scoring System

NACFC 2015
Oct 8-10, 2015; Phoenix, AZ, USA

POSTER

Modeling the Intermediate Health Outcomes of Patients with CF Who are Homozygous for the F508del CFTR Mutation Treated with Lumacaftor and Ivacaftor Combination Therapy

ECTRIMS 2015
Oct 7-10, 2015; Barcelona, Spain

POSTER

Risk of Self-harm and Suicide in People Admitted to Hospital with Multiple Sclerosis: A Record-linkage Study
Ramagopalan SV, Goldacre R, Goldacre MK

IDWeek 2015
Oct 7-11, 2015; San Diego, CA, USA

POSTERS

Clinical and Economic Burden of Hospitalized Patients with Serious Infections due to Carbapenem Resistant Enterobacteriaceae (CRE)
Wang R, Lodise TP, Bhagnani T, Zhao Q, Bhurke S, Berger A

Patterns of Empiric Antibiotic Therapy among Hospitalized Patients with Complicated Intra-Abdominal Infections (cIAI) or Complicated Urinary Tract Infections (cUTI) due to Enterobacteriaceae
Bhagnani T, Lodise TP, Wang R, Bhurke S, Zhao Q, Berger A

NAMS 2015
Sep 30-Oct 3, 2015; Las Vegas, NV, USA

POSTERS

An Approach to Improving the Care of Women Aged 45 to 64 through the Implementation of a Women’s Health Assessment Tool and Clinical Decision Support Toolkit (WHAT/CDS)

PSYCHOMETRIC ASSESSMENT

Evaluating the Reliability and Validity of the ANMS Gastroparesis Cardinal Symptom Index-Daily Diary in Patients with Diabetic and Idiopathic Gastroparesis
Revicki DA, Parkman HP

Preference for Pharmaceutical Formulation and Treatment Process Attributes
Stewart KD, Matza LS, Johnston JA, Curtis S, Gelhorn H, Havel H, Sweetana S

Psychometric Assessment of the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) Questionnaire in Patients with Relapsed and Refractory Multiple Myeloma (RRMM) Receiving Carfilzomib Treatment
Bacci E, Cocks K, Hurley D, Panjabi S, Revicki D

Qualitative Development of a New Clinician Reported Measure of Multiple Sclerosis Status
Phillips GA, Matza LS, Stewart KD, Jordan JB

Qualitative Equivalence between Paper and Electronic Tablet Versions of 8 PRO Instruments for Osteoarthritis
Eremenco S, Stringer S, C utts K, Iacobelli M

ORAL PRESENTATIONS

Measurement Properties of the Female Sexual Function Index Desire Domain in Women with Female Sexual Arousal Disorder
Wilson H, Jordan R, Spana C, Revicki D

Validation of a Crosswalk between Measures of Work Role Limitations
Anatchkova M, Kini N, Ware J, Bjorner J

The Evidence Forum 43
Outcomes Assessment of Implementing the Women’s Health Assessment Tool and Clinical Decision Support Toolkit (WHAT/CD5) within an Integrated Delivery System


ERS International Congress 2015
Sep 26-30, 2015; Amsterdam, Netherlands

ORAL PRESENTATION
A Novel Approach for Identifying Patients with Undiagnosed Clinically-Significant COPD

Martinez F, Mannino D, Leidy NK, Malley KG, Bacci ED, Barr RG, Bowler RP, Han MK, Houfek JF, Make B, Meldrum CA, Rennard S, Thomashow B, Walsh J, Yawn BP

ECCO - ESMO European Cancer Congress
Sep 25-29, 2015; Vienna, Austria

POSTERS
Life after Clinical Trials - Difficulties in Assessing Value of Drugs in Advanced Oncology

Benedict A, Muszbek N

Long-Term Clinical Experiences of Patients with Non-Small Cell Lung Cancer (NSCLC), Renal Cell Carcinoma (RCC), or Metastatic Melanoma: A SEER-Medicare Analysis


The Burden of Opioid-Induced Constipation among Patients with Cancer Pain and Patients with Non-Cancer Pain

LoCasale R, King F, Margolis MK, Coyne K

IMW International Myeloma Workshop
Sep 23-26, 2015; Rome, Italy

POSTER
Health Resource Utilization with Continuous Lenalidomide Treatment in Elderly Patients with Newly Diagnosed Multiple Myeloma


Patient Population with Multiple Myeloma and Transitions across Lines of Therapy in the United States: an Epidemiologic Model

Cid Ruzafa J, Merinopoulou E, Baggsley RF, Leighton P, Werther W, Felici D, Cox A

AAPManagement 26th Annual Meeting
Sep 17-20, 2015; National Harbor, MD, USA

POSTERS
Differentiating Chronic Pain Types


Prevalence of Self-Reported Chronic Pain in Primary Care


ICAAC/ICC 2015
Sep 17-21, 2015; San Diego, CA, USA

POSTERS
Costs to Treat Serious Infections Due to Carbapenem-resistant Enterobacteriaceae in United States (US) Hospitals

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

Length of Stay (LOS) in Hospital Associated with Empiric Use of Antibiotics with Microbiologic Activity against Carbapenem-Resistant Enterobacteriaceae (CRE)


ASPMN 25th National Conference
Sep 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

PAINWeek 2015
Sep 8-12, 2015; Las Vegas, NV, USA

POSTERS
Characterizing Healthcare Resource Utilization and Costs Based on Prior Utilization Patterns of Immediate-Release Hydrocodone


Does the Impact of Opioid-Induced Constipation Differ by Type of Chronic Pain?

Datto C, LoCasale R, Wilson H, Coyne K

Opioid Treatment Patterns for Patients Prescribed Immediate-Release Hydrocodone

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

Psychometric Validation of the Electronic Chronic Pain Questions in a Primary Care Setting


ISPOR 5th Latin America Conference
Sep 6-8, 2015; Santiago, Chile

WORKSHOP
Understanding the Impact on Patient Access and International Reference Pricing in Latin America

Guarin D, de Bustamante MM, Alfonso R, Caro JJ

ISSP Annual Symposium
Sep 1-4, 2015; Lyon, France

POSTER
Development and Reliability Assessment of the MPS II Disease Severity Score (DSS)


ESC European Society of Cardiology Congress
Aug 29-Sep 2, 2015; London, UK

POSTERS
A Simulated Head-to-Head Comparison of Stroke and Major Bleeding with Apixaban versus Rivaroxaban in High-Risk NVAF Patients


Comparative Cost-effectiveness of Oral Anticoagulants for Stroke Prevention in Non-valvular Atrial Fibrillation Patients in the UK

Lip GYH, Lanitis T, Kongsakorn T, Phatak H, Liu L, Lawrence J, Dorian P

Potential Clinical Benefits and Cost Savings Associated with Inclusion of Apixaban in the Formulary for Treatment of Patients with Venous Thromboembolism

Hamilton M, Leipold R, Rublee D, Stern S, Gabriel D, Gossden T, Cohen A

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Evidera has a new software platform designed to support near real-time analyses of virtually any type of real-world data source, including claims, electronic medical records, and registry data. Evalytica™ uses standard data formats and published analytic methods that provide transparency and yield results that may be used in publications or submissions.

“Evalytica™ marks a new frontier for Evidera as a leader in technology enabled tools for generating and communicating evidence of product safety and effectiveness,” said Jon Williams, President and CEO, Evidera. “The increasing focus on real-world evidence for drug safety analysis that has resulted from the FDA Sentinel, the Observational Medical Outcomes Partnership (OMOP), and the Observational Health Data Sciences and Informatics (OHDSI) initiatives make tools like Evalytica™ that much more important.”

Evalytica™ contains a growing repository of pre-built Analysis Apps that provide extensive analytic capabilities in areas such as drug safety, epidemiology, health economics, and comparative effectiveness, along with a programming interface for custom Analytic App development. Collaboration features, such as a library of reusable patient cohort and health outcome definitions that can be curated, searched, shared and re-used across users and analysis communities, foster collaboration and sharing based on an area of common interest, such as therapeutic area, pharmaceutical product, or research project.

Designed by a team of industry pioneers, Evalytica™ builds upon the strengths of previous real-world analytics technologies while also addressing their weaknesses. “Being able to draw upon one of the most well-respected research teams in the life sciences industry has been a tremendous advantage for us in developing Evalytica™,” said Stephanie Reisinger, Vice President of Technology Solutions, Evidera. “Evalytica™ provides an option for users to connect directly with Evidera scientists to get help with database selection, cohort definition, analysis methodology, results interpretation or any other question associated with an analysis.”

To schedule a demo of Evalytica™, or for more information, please email info@evidera.com or visit www.evalytica.com.
Evidera Welcomes Dr. Bryan Luce as a Senior Advisor

Evidera is pleased to announce that Bryan Luce, PhD, MBA, has joined Evidera as a Senior Advisor. In this role Bryan will provide thought leadership and strategic guidance to the Evidera executive leadership team, as well as counsel to Evidera’s global clients and other industry collaborators.

Bryan comes to Evidera from the Patient-Centered Outcomes Research Institute (PCORI), where he served as their Chief Science Officer, leading the development and implementation of PCORI’s patient-centered comparative clinical effectiveness research (CER) agenda. Prior to his time with PCORI, Bryan served as senior vice president for science policy at United BioSource Corporation (UBC), and founded the outcomes research firm MEDTAP International, serving as its chairman, president, and chief executive officer before its acquisition by UBC in 2004. Evidera was divested from UBC by its parent company Express Scripts in 2013.

“Bryan has always been an important part of this organization, serving not only as one of our founders but also as one of the pioneers who helped build and shape our field,” said Jon Williams, President and CEO, Evidera. “We’re incredibly excited to welcome Bryan to the Evidera family, and to work alongside him as he continues to build and leverage his expertise in comparative effectiveness and patient-centered outcomes research.”

Bryan has focused the bulk of his career on developing and improving methods, policies and applications for evidence-based healthcare. In 2008, he founded the Pragmatic Approaches to Comparative Effectiveness (PACE) Initiative, a collaborative effort to study and improve the methods used for comparative effectiveness trials to better meet the needs of payers, policy makers and clinicians. He has also served in leadership roles with Battelle, the Centers for Medicare and Medicaid Services, and the Office of Technology Assessment of the United States Congress.

“I’m truly humbled to join such a talented group of scientists and consultants, and I’m excited about what the future holds for Evidera,” said Bryan. “I have been fortunate to work with many great minds and wonderful people over the course of my career, and I have no doubt that I will continue to do so with Evidera.”

Bryan has authored more than 100 scientific publications, including three textbooks on health technology assessment, health policy, and health economics. He has been an advisor to numerous government and nonprofit agencies, as well as pharmaceutical and device firms worldwide. He also served as the fifth president of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), and received their Avedis Donabedian Outcomes Research Lifetime Achievement Award in 2008.

Bryan will continue to consult for PCORI and other organizations, and expects to be active as an affiliate research professor at the University of Washington.

For more information, please contact info@evidera.com, or to reach Bryan directly, please email Bryan.Luce@evidera.com.
Evidera recently announced the release of the first Alzheimer’s Disease ACE simulator. Bringing to bear more than two decades of experience in modeling Alzheimer’s disease (AD), Evidera scientists have developed the AD ACE, a comprehensive multi-application disease simulator designed to address evolving commercial and regulatory needs.

“We are very excited about the AD ACE and what it brings to the field. It is the only model in AD specifically designed to assess interventions from the earliest stage of disease, including the transition from normal cognitive function, through to severe disease,” said Jaime Caro, Evidera’s Chief Scientist. Dr. Caro will be presenting the AD ACE model at the upcoming International Pharmacoeconomic Conference on Alzheimer’s Disease, November 19-20 in Boston, MA, USA.

AD ACE was designed to address the complex interactions between multiple components of AD pathology (e.g., biomarkers, cognition, behavior, function) and their role in disease progression. It also fully considers interrelated clinical, epidemiologic, and economic outcomes, providing a platform that will allow for rapid incorporation of intervention-specific data.

Programmed in MS Excel®, the AD ACE is very transparent and meets health technology assessment (HTA) agency requirements for formal submissions. It can also be used by internal stakeholders and other decision makers. It is readily modified to meet the specific features of the therapy or diagnostic of interest and will support commercial strategy development, inform clinical trial design, and allow for a variety of economic analyses. AD ACE is driven by the latest science in this field and is extensively validated and well documented.

To gain access to the AD ACE, or for more information, please email info@evidera.com or visit www.evidera.com/ACE.

Eric Faulkner Joins Evidera as Executive Director, Emerging and Innovative Technology Solutions

Eric Faulkner, MPH, will be joining Evidera on November 1, 2015, as the Executive Director, Emerging and Innovative Technology Solutions. Eric brings approximately 17 years of experience in the healthcare industry focusing on value demonstration, product commercialization, and market access/reimbursement. In this new role at Evidera, he will be focusing on health technologies with significant disruptive potential which have complex access issues or requirements such as personalized medicine, diagnostics, combination products, e-technologies, cell therapy, and regenerative medicine.

Prior to joining Evidera, Eric held several senior level positions at Quintiles, including Practice Leader, Emerging Technology Value Demonstration, Access and Commercialization and Principal, Global Market Access and Commercialization, where he developed and led a cross-functional practice including clinical, late-phase, and commercial business units focused on emerging technology product support. He has also held roles at RTI Health Solutions, Littell Group, Inc., and The Lewin Group where he was responsible for evidence-generation solutions to support the approval and market access of pharmaceutical and medical device products.

Eric’s prior project work has included global market strategy analysis, qualitative and quantitative research, evidence-based practice and policy, design of clinical trials to meet third-party decision requirements, life sciences portfolio due diligence, and modeling/decision support. He has led health policy assessments, including CMS’s Coverage with Evidence Development (CED) and Clinical Trial Policy, value-based purchasing, competitive bidding, cost-effectiveness, comparative effectiveness, and pharmacogenomics for life sciences manufacturers, industry, medical professional associations, and government agencies. He has also served as a global payer expert for emerging technologies for various global industry and EU government groups.

Eric is a recognized global thought leader in the specialty areas mentioned with extensive publications and over 70 global panel sessions on these topics. He has recently served as an expert advisor to the Personalized Medicine Subcommittee of the President’s Council of Advisors on Science and Technology and advised the Austrian government on personalized medicine policy for oncology. He serves as an adjunct Assistant Professor for the Institute for Pharmacogenomics and Individualized Therapy at the Eshelman School of Pharmacy of the University of North Carolina at Chapel Hill and as the Executive Director of the Genomics Biotech and Emerging Medical Technology Institute of the National Association of Managed Care Physicians.
The Evidence Forum is an official publication of Evidera, addressing the scientific and strategic challenges of today's healthcare environment and providing a forum for the exchange of thoughts and ideas focused on evidence and value.