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Rare Disease Treatments Aren't So Rare Any More

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Over 350 million people worldwide suffer from a rare disease. One out of every two of those diagnosed with a rare disease is a child. Eighty percent of rare diseases are caused by a faulty gene. Ninety-five percent of rare diseases have no FDA-approved treatments.[1] The need to find cures and therapies for these afflictions is overwhelming, and the potential for our industry to have an impact is staggering.

While the number of treatments has grown, the path to evidence generation, approval, and access remains uniquely challenging.

- A widely divergent spectrum of diseases are potential targets for life-changing therapies, however, many of these are characterized by an absence of widespread clinical knowledge of disease natural history, consensus on clinical endpoints, and development and regulatory precedent.
- Widely dispersed patient populations, who often have a high disease burden and significant medical challenges, must be identified, accessed, and engaged to design and execute successful clinical development and access programs.
- Clinical programs can be data intensive and logistically complicated, and are often conducted at research naïve sites, presenting significant management hurdles which must be proactively identified and addressed.
- And finally, because children and adolescents represent at least half of patients affected by rare diseases, development programs must address the specific needs and protections specific to pediatric patients.

Despite these challenges, there are a myriad of innovative and tailored solutions being developed that can help to generate the evidence needed for successful approval and access. In this issue of *The Evidence Forum*, our thought leaders provide insights on many of the important issues and novel solutions affecting the path to market for these special treatments, such as: the changing regulatory landscape (e.g., the US Food and Drug Administration's recent updated draft guidance on rare diseases); incorporating patient-perspective; choosing the right clinical outcome assessments (COAs); the implications of the new EU-HTA process; and, the application of innovative data collection methods.

As this segment of the industry continues to grow, success will depend on keeping an open mind and adapting to the shifting landscape as knowledge increases, new discoveries are made, and expectations and requirements evolve. Now more than ever it is critical to plan early, develop an evidence strategy that considers both regulatory approval and market access, and commit to understanding the nuances of this dynamic space. As Marcel Proust said: "The real voyage of discovery consists not in seeking new landscapes, but in having new eyes." ■

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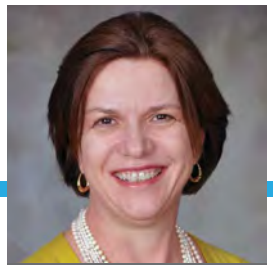

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FDA Updates Draft Guidance on Rare Diseases
Some Key Takeaways You Need to Know

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In January 2019, the US Food and Drug Administration (FDA) released new draft guidance on rare diseases (*Rare Diseases: Common Issues in Drug Development, Guidance for Industry*[1]), which replaces the guidance on rare diseases previously released in 2015 (*Rare Diseases: Common Issues in Drug Development*, August 2015). Since rare diseases are a fast-growing and important target for new drug development, some of the key implications of this guidance for pharmaceutical companies developing products for this context of use are outlined below.

Rare diseases were defined in the Orphan Drug Act (ODA) of 2010 as diseases that affect fewer than 200,000 patients, although many of them afflict far fewer numbers. Several factors contribute to the challenges of bringing new drugs to market for these diseases, including: a) they are predominantly (up to 75%) diseases that afflict children; b) very small sample sizes available for studies create challenges in using traditional statistical and study design methodologies; and, c) considerable clinical challenges – such as unique symptom clusters, or symptoms that may mimic other diseases – thus making diagnosis difficult. Traditional methodologies for validation and statistical analysis are particularly challenged. An excellent introduction to the general issues for outcomes researchers in rare diseases can be found in the ISPOR COA Good Practices Task Force Report on Rare Diseases (Benjamin et al., 2017).[2]

This article highlights several topic areas from the new draft guidance that may be of particular interest to outcomes researchers and drug developers.

William R. Lenderking

1. **The importance of protocol-driven, prospective, natural history studies is emphasized,** and since there is often not a great deal known about rare diseases, these studies are particularly relevant. Understanding the natural history is essential to:
   a. Defining the disease population to be studied
   b. Selecting the appropriate outcome measures
   c. Helping establish study design parameters such as length of follow-up and frequency of evaluation
   d. Developing biomarkers

   One passage in the discussion of rare diseases (lines 151-155) is particularly pertinent to patient-centered researchers in helping to identify "signs and symptoms that are most important to patients." It goes on to make a related point, which is that it is important to "collect … reports of patient functioning and feeling." An example of this type of work can be found in a recent publication about the adaptation and validation of a new measure of functional outcomes in the rare disease Pantothenate Kinase-Associated Neurodegeneration (PKAN) based on UPDRS-2, originally developed for Parkinson's Disease. (Marshall et al., 2019).[3]

   (For more information, see "Natural History Studies in Rare Diseases and Genetic Biomarkers" by Bevan et al. and "Registries in Rare Disease Research – Approaches to Optimize Success" by Ross in this issue of *The Evidence Forum*.)

2. **Issues of study design are raised.** Although the guidance does not specifically mention statistical or design issues, referring the reader to previous guidance published by ICH (*E9 Statistical Principles for Clinical Trials* [September 1998] and *E10 Choice of Control Group and Related 77 Issues in Clinical Trials* [May 2001]), special considerations are required to statistically analyze and make robust inferences about data from very small samples. The guidance does mention that in some cases, such as when it may be unethical to have a placebo arm, a well-designed natural history study can serve as an external control for a clinical trial, a very pragmatic recommendation in this setting (lines 140-141). The guidance also suggests that adaptive designs which allow data collected early in the study to be used later in the study may be applied under certain circumstances (lines 419-424).

3. **Given small sample sizes, it can be essential to use well-known outcomes measures where possible** (preferably those with norms developed for their use, or at minimum responder definitions to help interpret the meaning of scores). An example of this can be found in a recently published, cross-sectional burden of illness study in another rare disease (hATTR-FAP) (Stewart et al., 2018).[4]

4. **Adaptation of clinical outcome assessments (COAs) are suggested.** Since many rare diseases may have certain aspects that are similar to other more common diseases, even though the underlying metabolic pathway may be quite different, outcomes researchers may be involved in adapting existing COAs for a new context of use, rather than developing new instruments, as in the work cited above by Marshall et al.[4] (Also see "Adapting an Existing Instrument for a Rare Disease – A Valuable Resource within Your Reach" by Murray and Bacci in this issue of *The Evidence Forum*). Clinical outcomes rather than surrogate markers remain the most common way with which drugs are evaluated (lines 400-402).

5. **The Agency suggests several ways to improve the reliability of assessment and diminish the possibility of bias in clinical evaluations,** including rater training, and even blinded, centralized ratings (lines 445-451).

6. **Safety evaluations** may, in certain conditions, be facilitated through direct, systematic reports from patients, as is being done increasingly in oncology studies, for example, using the Patient Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE) (Basch et al., 2014[5]; Speck et al., 2018[6]).

7. **Finally, the role of direct engagement with patients with rare diseases** can greatly facilitate both scientific accuracy and operational efficiencies in terms of identifying outcomes meaningful to patients and finding patients willing to participate in experimental studies. In lines 728-730, under Additional Considerations, the FDA recommends direct communication between sponsors and patients regarding "potential endpoints and meaningful changes."

Treatments for rare diseases continues to grow at a rapid rate, with more than 600 orphan drugs being approved by the FDA since the passage of the Orphan Drug Act in 1983, and 560 medicines in clinical development for the treatment of rare diseases.[7] And while there are over 7,000 different rare diseases that have been identified to date, only 5% of those diseases have treatments.[7,8] With 350 million people suffering from a rare disease globally,[8] the emphasis on developing treatments for these indications has grown significantly. In the US, 41% of all new medications approved by the FDA in 2016 were orphan drugs to treat rare diseases,[9] and in the EU, 1,900 medicines were granted orphan status by the end of 2017, with 140 orphan medicines marketed in the EU as of August 31, 2018.[10]

The FDA's updated draft guidance on rare diseases indicates a continued interest in providing sound recommendations in support of providing a way forward for companies developing treatments for those suffering with rare diseases. FDA Commissioner Scott Gottlieb, MD, recently stated "The FDA is committed to supporting the development of treatments for patients with rare diseases and has been focused on advancing policies that will help enable these opportunities. We know that developing a drug or biologic for a rare disease can be especially challenging, which is why it's important that the FDA continues to provide clear information to drug developers so that they can plan modern, efficient drug development programs that will be successful."[11]

The guidance also aligns with FDA's commitment to more patient-focused drug development with the inclusion of several points related to patient outcomes, COA adaptation, and direct patient engagement. There are some very important issues addressed in the updated draft guidance that are very relevant to, and supportive of, early evidence planning, inclusion of the patient perspective, and real-world studies to supplement clinical data – all of which can be vital aspects of a complete evidence package that is often unique to rare disease treatments receiving regulatory approval and market access. ■

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Patient Engagement in Clinical Trial Protocol Design and Recruitment Strategies

What Does It Mean for Orphan Drug Manufacturers?

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Introduction

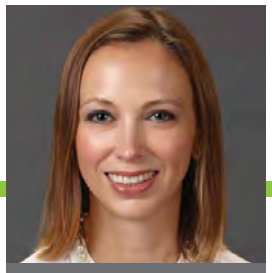
The last 10 years have seen the complexity of clinical trials increase - the number of procedures involved in trials has increased by 59% and planned visits have increased by 25%.[1,2] This complexity has coincided with declining numbers of patients who are eligible and recruited per site, increasing the need for a larger number of investigative sites and countries in which drug makers are conducting trials.[2] In that context, it is perhaps unsurprising that a third of trials fail to meet their recruitment targets, and more than half of trials need to be extended to do so.[3]

Trials are correspondingly either underpowered or more costly and time intensive to conduct.

These issues are compounded in rare disease populations where recruitment difficulties can arise for several reasons, including:

- Small populations distributed over wide geographic areas
- Many rare diseases being paediatric
- Patients often being highly frail
- There being few centers for diagnosis
- A scarcity of investigators focused on these rare diseases[4]

Kevin Marsh



Margaret Vernon

Furthermore, there is often little, if any, experience of conducting studies with rare disease populations, meaning a lack of knowledge about which trial designs work for these special populations. To conduct a successful trial program, it is imperative that trials are designed and implemented in such a way as to enhance patients' and caregivers' experiences and reduce burden and complexity. This is likely to be particularly true in a rare disease population, which may require some special accommodation in order to participate in the trial and can be facilitated by engaging patients in the design of trials. Patient engagement has become a hot topic in recent years, and many high-profile initiatives have advocated for and facilitated patient engagement in research and decision making throughout the drug development process.[5-8] In January 2019, the US Food and Drug Administration (FDA) published its draft guidance on rare diseases, *Rare Diseases: Common Issues in Drug Development Guidance for Industry*, which includes a section on the importance of patient and caregiver engagement in rare disease clinical trials to ensure patients' and caregivers' perspectives about experiences, expected and desired outcomes of treatment, and needs are taken into account.[9]

> To conduct a successful trial program, it is imperative that trials are designed and implemented in such a way as to enhance patients' and caregivers' experiences and reduce burden and complexity.

Key stakeholders have acknowledged the important role that patients can play in the design of clinical trials for treatments for rare diseases. For instance, the National Institutes of Health (NIH) Office for Rare Disease Research (ORDR) established the Rare Disease Clinical Research Network (RDCRN). The RDCRN was unique in being the first program that created a collaborative and coordinated network of investigators and patient groups to support research into rare diseases. The network comprises 22 research consortia, of which 82% report patient groups reviewing protocols and providing substantial input on study design, and 94% report patient groups reviewing study forms and other study related documents.[4]

More recently other rare disease organisations have encouraged the involvement of patients in the design of clinical trials in rare diseases. EURORDIS-Rare Diseases Europe has published a charter for the collaboration between study sponsors and patient organisations, with the aim of improving the quality of clinical research in rare diseases,[10] and Genetic Alliance has published a guide for sponsors and investigators on involving patients in clinical research.[11]

How can patients be engaged in trial design and implementation?

Engaging patients in trial design and implementation plans can help ensure:

- The patients included in trials are those that are likely to have a positive benefit-risk balance
- The endpoints included in the trial capture experiences and outcomes of treatment most important to patients
- The trial is conducted in such a way as to enhance experience and ease burden

We specifically focus this paper on the experience of and burden on the patient participating in the trial.

Patients can be instrumental in providing input on designs and operational implementation of trials that enhance enrollment and retention. Patient input on protocol design can identify potential barriers to participation and retention and support development of appropriate solutions, such as:

1. Modifying design elements of the trial to ensure that patients think there is value in the study objective
2. Development of key messages and outreach materials to enhance enrollment
3. Development of logistical support, such as transportation, in the case of obstacles such as format, location, scheduling, length, and timing of assessments
4. Engagement and retention strategies – such as providing patient-friendly communications, gamification, or incentives – in the case of a trial design that has been identified as lengthy or potentially burdensome
5. Tailoring solutions to ensure the feasibility of trial participation in specific populations, perhaps identified by geographic location

Figure 1 summarizes methods that have been adopted to elicit patients' input into protocol design. Involving patients as partners ensures that their views are available as part of the research team, which is insightful in itself but can also enhance implementation of other engagement activities. One-on-one interviews and focus groups can provide an in-depth characterization of the patient experience and perception of trial designs. Simulations, such as mock trial visits, may help patients and other stakeholders understand what is involved in a trial and allow them to comment on the relative burden or potential barriers to participation or adherence with trial procedures. Quantitative methods, such as surveys embedded in trials, can characterize the clinical trial experience for a broader set of patients and help to inform trial interpretation or future trial designs. Crowd sourcing can offer feedback on elements of the protocol from a larger, more diverse sample. Finally,

Figure 1. Methods for Eliciting Patient Input into Protocol Design

Patient Partners	Quality Research	Simulation	Quantitative Research
• Patient advocate as part of design team • Patient advisory board	• Focus groups • Interviews	• Mock trial visit	• Embedded surveys as part of trials • Crowd sourcing • Preference methods

preference methods can be used to understand the burden that trials place on patients. For instance, running choice experiments with patients – giving them pairs of trials each characterized by different time and travel commitments, and involving different numbers and types of assessments – allows us to understand how changing the design of a trial will impact the probability that a patient will participate, and how this varies between different groups of patients.

What are the benefits of involving patients in trial design and implementation planning?

As a relatively new practice, there is limited public evidence on the time and cost savings of gathering patient input on protocol design, particularly in rare diseases. A recent review of patient involvement in the rare disease product development process concluded that, to date, patient opportunities for involvement in clinical trials have solely comprised enrollment as trial subjects,[12] and involvement in the design of trial has been confined to patient organizations (for instance, see those mentioned in the introduction).

Nevertheless, the evidence that does exist is encouraging. First, a recent review published in the *BMJ* identified 26 studies on the impact of patient or public engagement on study enrollment and retention.[13] Nineteen of the studies were eligible for a meta-analysis of enrollment rates, and five for a meta-analysis of retention rates. The review concluded that patient and public engagement in study design increases the odds of participant enrollment. No impact was identified on retention rates, due to the smaller sample of studies addressing retention rates, and the nature of interventions varying between studies.

Second, the expected net present value (ENPV) of patient engagement in a typical oncology development program entering Phase II or Phase III has been modeled.[14] Assuming that a protocol review with a patient group results in the avoidance of one amendment, the authors estimate patient engagement increases the ENPV at pre-Phase III by $75 million. Put another way, a $100,000 patient engagement exercise would only have to reduce the probability of needing an amendment by approximately 0.1% before it justified its cost. That is, the costs of gathering patient input on protocol design are relatively low compared to the potential benefits: every time a patient drops out of a study, it can cost up to $36,000 to add a new patient, sometimes requiring the opening of new sites depending on dropout rates.[15]

Finally, analyses of trial databases, such as Trialtrove® and Pharmaprojects®, suggest that drugs developed with patient-centric designs are:

1. Quicker to recruit 100 patients (4 months) than drugs developed without such designs (7 months)
2. More likely to be launched (87%) than drugs developed without such designs (68%)[16]

Conclusion

In summary, involving rare disease patients and their caregivers in drug development, and particularly protocol design and operational implementation planning, could provide myriad benefits to the trial sponsor and the target patient and caregiver community at large. Benefits for sponsors include faster enrollment and reduced drop out, including associated costs. Perhaps the greatest benefit is for the patients, including reducing the hurdles to participating in trials, reducing unnecessary burden and complexity for patients participating in trials, and getting drugs to market faster for patients who need them the most. ■

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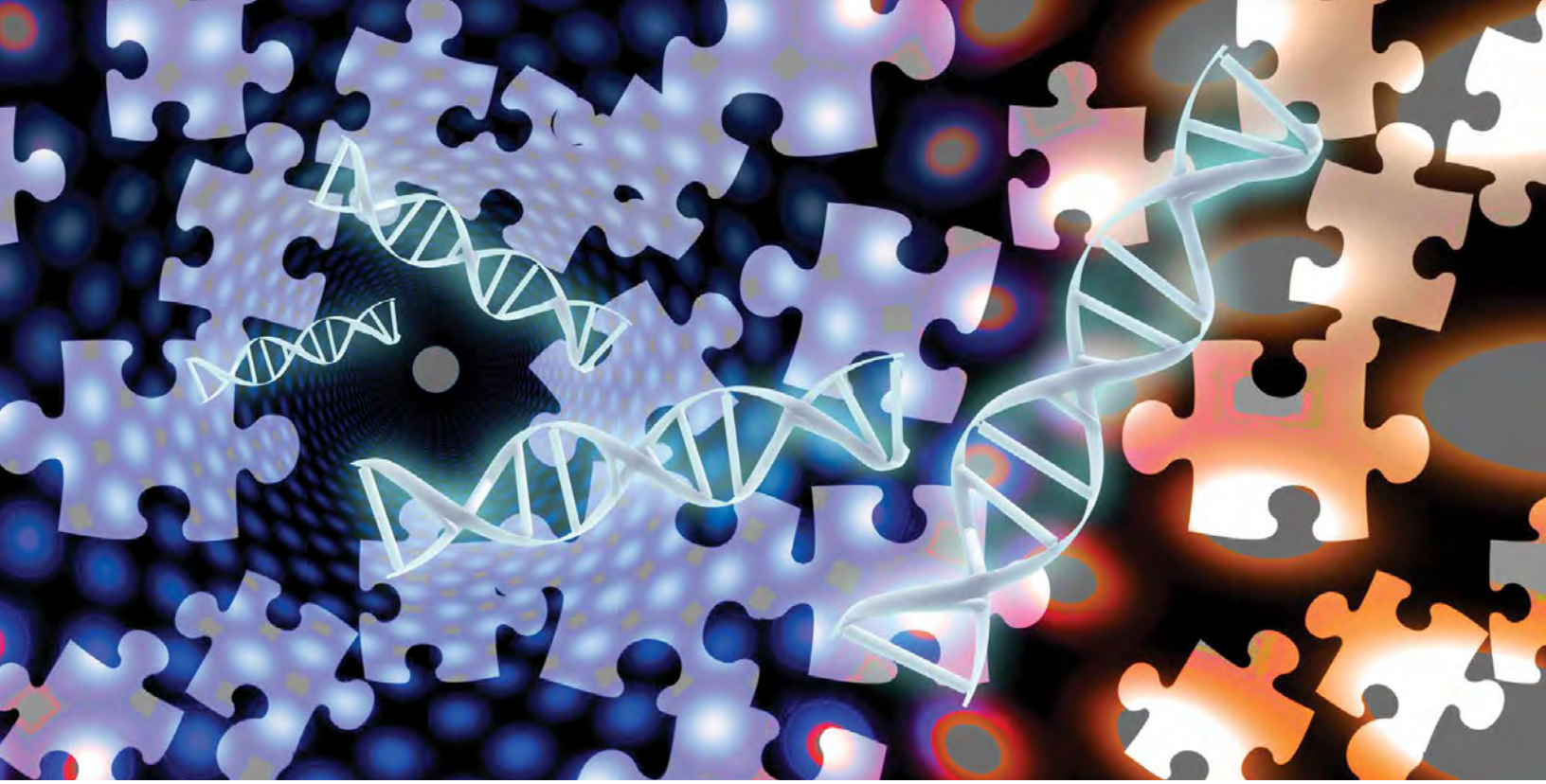

Natural History Studies in Rare Diseases and Genetic Biomarkers

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Introduction

The increasing development of orphan drugs and precision medicine has led to novel needs in terms of real-world evidence generation. A key area recently highlighted in the FDA's updated draft guidance on rare diseases[1] is the recommendation of natural history studies to better characterize patient populations and delineate target populations. Natural history studies are epidemiological studies that focus on describing the frequency, features, and evolution of a disease by collecting real-world data from groups of patients suffering from this disease. These studies are often performed by biotech and pharmaceutical companies early in the clinical development process to support and guide the design of clinical trial and drug development studies.

In the last few years, natural history studies have started to include genetic testing to describe specific genetic


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profiles as part of the features of the patient population, or as a screening criterion to identify the target population. The introduction of genetic testing within a fully non-interventional setting poses regulatory and ethical issues that are addressed differently by approval bodies (ethics committees, regulatory agencies, privacy committees, etc.) across the globe, highlighting the need for ongoing interpretation of the current regulations.

Natural History Studies and Genetic Biomarkers

Increased focus on rare diseases and precision medicine

The recent wave of new product introductions in rare diseases and precision medicine (including targeted oncology indications) has allowed improved outcomes for patients who would otherwise face grim prognoses. However, health system budgets have not necessarily adjusted to the high prices and to the increasing number of available therapies in these categories. This has led to a need for "triage" strategies that allow payers to select therapies that do the most good for the least utilization and cost.

There are many rare disease and advanced oncology therapies currently available, most of which are extremely costly. In 2018, the US approved 34 novel therapies for rare diseases, comprising 58% of new drug approvals last year[2]; this contrasts with 9 rare disease approvals in 2013 (See Figure 1).[3] According to EvaluatePharma,[4] rare disease and targeted oncology therapy sales are predicted to have 11-12% compound adjusted growth rates through 2024, which is more than double that for other prescription drugs. This growth is expected to continue as high financial returns will fuel more development and investment, which is expected to fuel more drug approvals and launches.

These factors combine to create a financial risk to payers. Consequently, payers manage the financial impact by restricting eligibility and reimbursement only to patients who are likely to have a significant benefit over standard of care.

The role of natural history studies in the drug development strategy

The increased attention from biopharmaceutical companies and payers on rare disease and orphan drugs means there is a greater need to be able to accurately define the profile, characteristics, and disease outcomes of the target patient populations. This is where natural history studies (See Panel 1) play a key role for both stakeholders.

Panel 1. Natural History Studies

Epidemiological Studies (do not involve evaluation of a specific therapy)	
Objective	Describe the frequency, features, risk factors, outcomes, burden, and/or evolution of a disease
Approach	Collect and/or analyze real-world data from groups of patients suffering from the disease of interest
Design	Often designed as a longitudinal cohort study or registry, however, study design can vary according to the disease of interest and study objectives among the following options: • Cross-sectional or longitudinal approaches • Prospective or retrospective designs • Primary or secondary data sources

Figure 1. US FDA Approvals of Novel Therapies

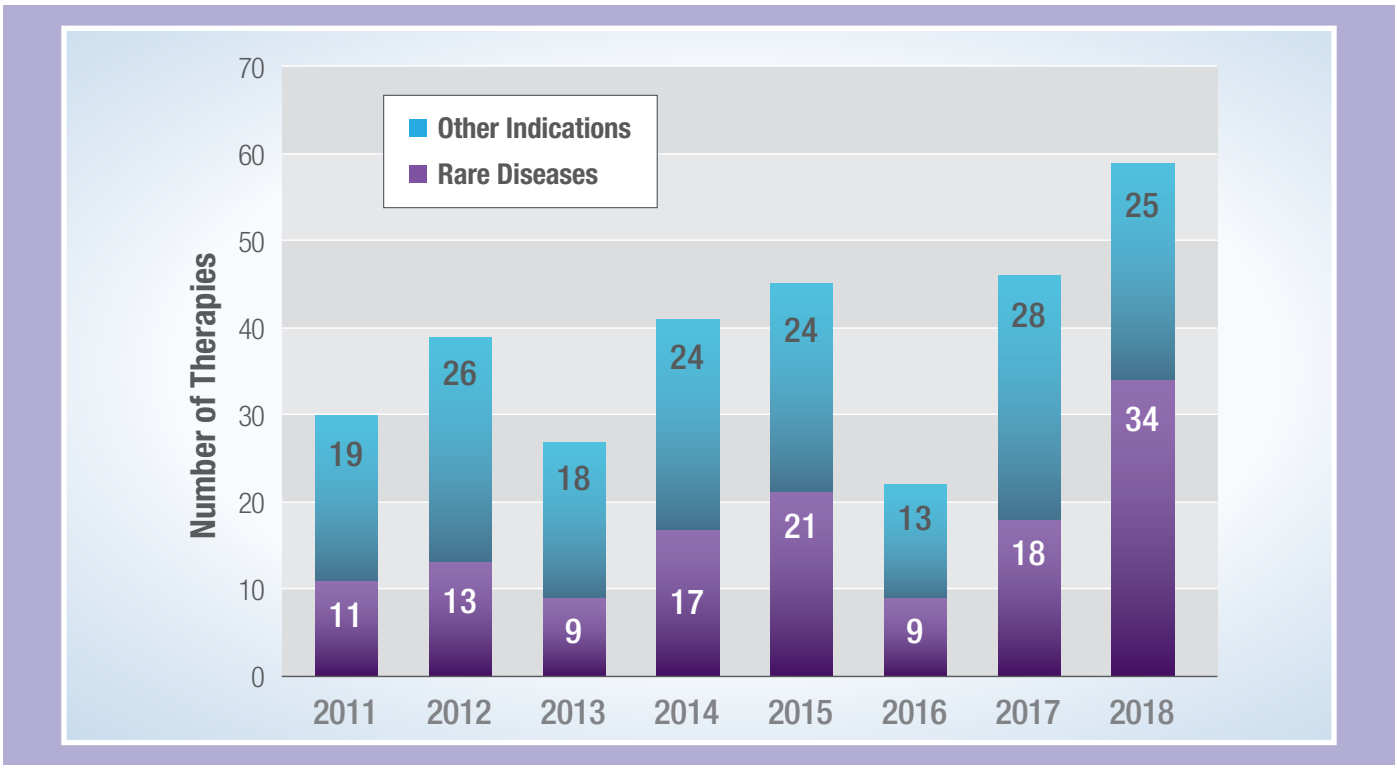
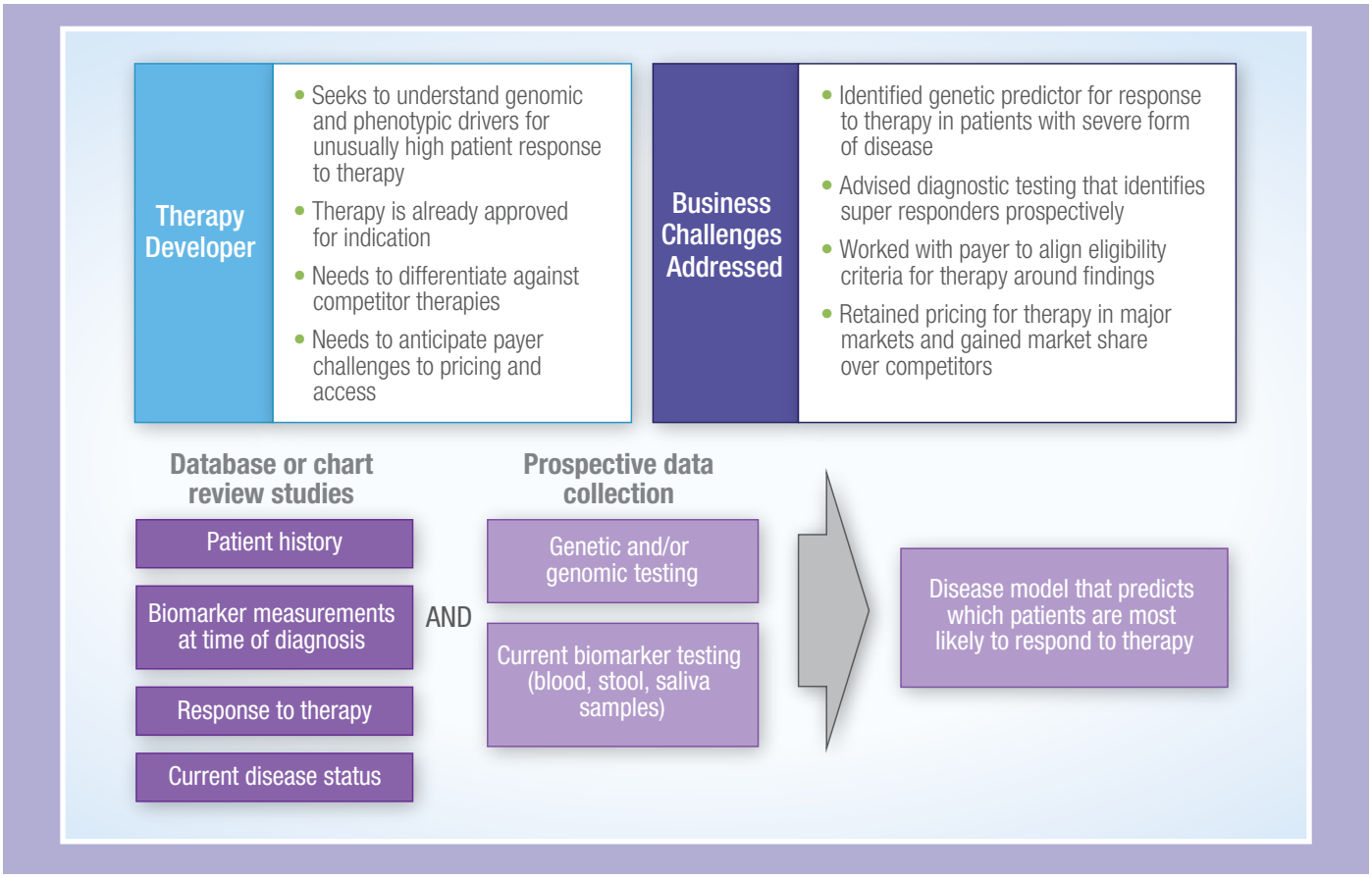


Figure 2. Case Study: Characterizing Potential Responders to Enhance Differentiation and Optimize Market Access



On one hand, natural history studies can inform clinical product development by:

- Providing better insights into disease characteristics, patient populations, and identification of disease subtypes
- Identifying the most sensitive and relevant endpoints or the optimal duration of follow-up
- Identifying patients eligible for clinical trials
- Serving as an historical comparator in case of single arm trials

On the other hand, natural history studies help payers "triage" care to patients most likely to benefit from therapies by:

- Assessing disease burden in real-world clinical practice under standard of care
- Identifying and describing sub-types of a disease that have a higher burden
- Identifying patient sub-populations who are less or more likely to respond to current therapies (See Figure 2)
- Identifying patient sub-populations that are likely to have the greatest benefit versus risk with new therapies

The emergence of genetic biomarkers in real-world evidence generation

Biomarkers are an integral part of natural history studies for rare disease and advanced oncology therapies. This is driven by the nature of the diseases since many rare diseases are caused by inherited genetic mutations. The number and specific type of mutations can be highly predictive of disease severity and response to treatment. There is also a trend towards identifying biomarker-based subgroups of patients suffering from a more common disease that could present with characteristics such as a worse prognosis or being difficult to treat and that could be identified as target populations for targeted treatments.

The FDA now considers biomarker identification or validation as a full part of natural history studies in rare diseases.[1] This introduces a new paradigm into the regulatory and operational aspects of running natural history studies.

Regulatory Interpretation of Genetic Testing in Natural History Studies

Non-interventional vs. interventional

Real-world evidence generation is clearly differentiated from clinical trials, with its main feature being that patients are treated and monitored according to routine clinical practice and not according to any study protocol-defined

procedures. However, in the perspective of maximizing the protection of patients, regulators and ethics committees have been issuing guidance around operationalization of real-world evidence generation. Regulations and guidance vary across geographies and are continuously evolving as new information becomes available and healthcare systems mature.

In practice, the main (but not unique) feature determining the classification of a real-world study as interventional or non-interventional is its objective and whether it focuses on observing the characteristics of a disease or on observing the effects of a drug.[5,6] Natural history studies are typically focused on observing the characteristics of a disease. However, the need for specific tests such as questionnaires or non-routine biological samples is potentially another criterion for classification and happens to be interpreted differently across geographies. Typically, genetic testing can be done either via buccal swab (considered non-invasive) or more often via blood sample (considered invasive). According to the disease being studied and the regional/local regulations, blood sampling may be considered either a routine diagnosis or monitoring procedure, or as a protocol-driven, non-routine procedure.

When setting up a natural history study, it is helpful to understand the probable classification of the study according to geography as well as the corresponding regulatory pathway for planning and organization purposes.

Genetic testing

There currently is no consensus definition of genetic testing, despite many organizations and governments who have voiced a desire for such an agreed upon definition. Furthermore, notable bodies such as the International Conference on Harmonization (ICH) and the US Food and Drug Administration (FDA) have not published any definitive guidance on genetic testing in the context of clinical research, therefore, it is not surprising that the implementation of regulations for genetic testing is diverse and confined to individual country statutes. There are some areas where consensus is emerging,[7] but clearly there is still much to be accomplished towards the harmonization of guidance and regulations.

Figure 3 visually summarizes the relevance and connection of the elements that drive the regulatory and ethics pathways, showing how study objectives, geography, and genetic testing all play a role in the type of studies required for treatments of rare diseases.

Other considerations

In addition, if the natural history study is to serve as historical control to a one-arm clinical trial, it is recommended to seek preliminary regulatory agency agreement to such designs ahead of submitting final protocol.

Figure 3. Drivers of the Regulatory and Ethics Pathways

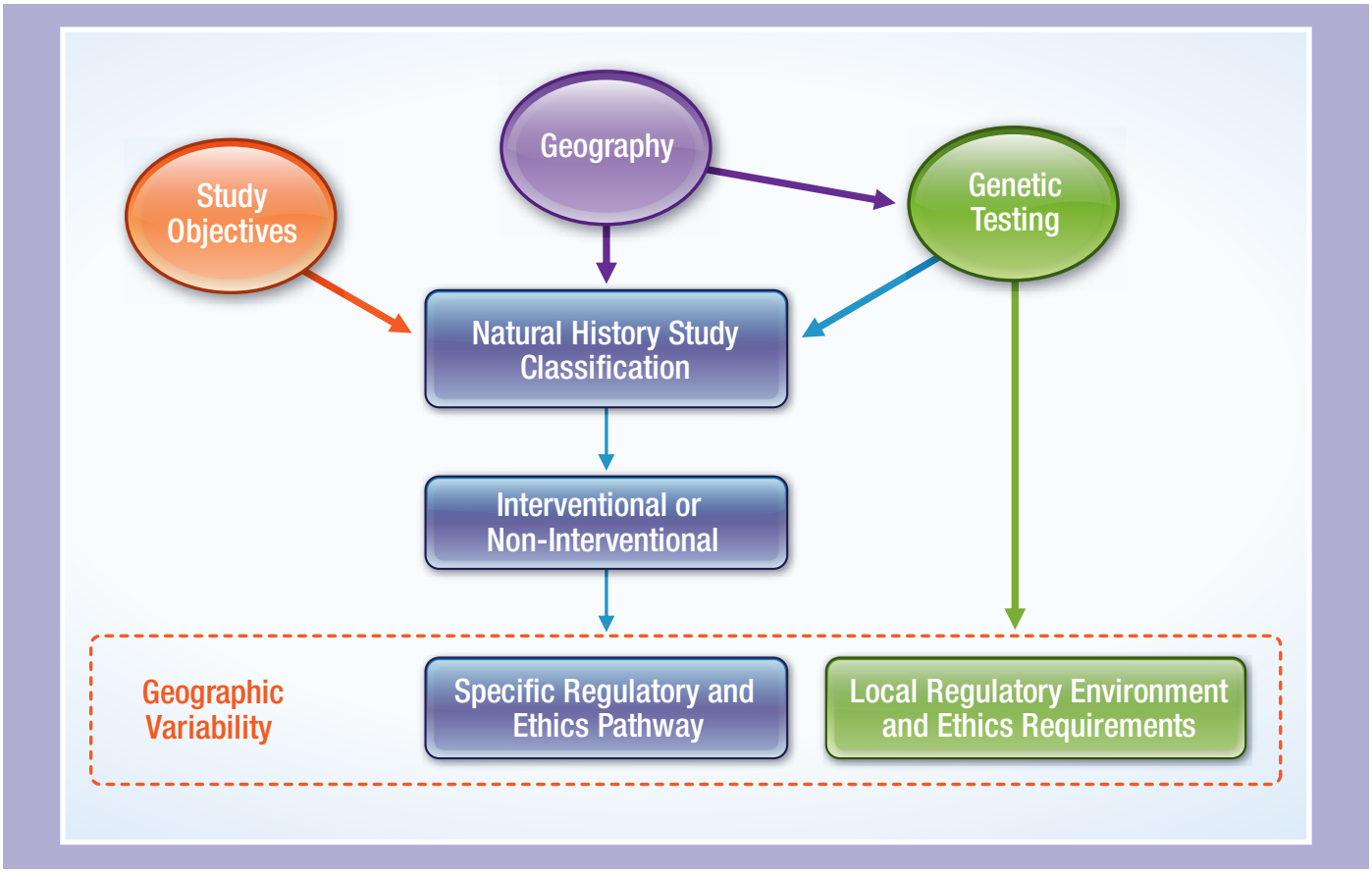
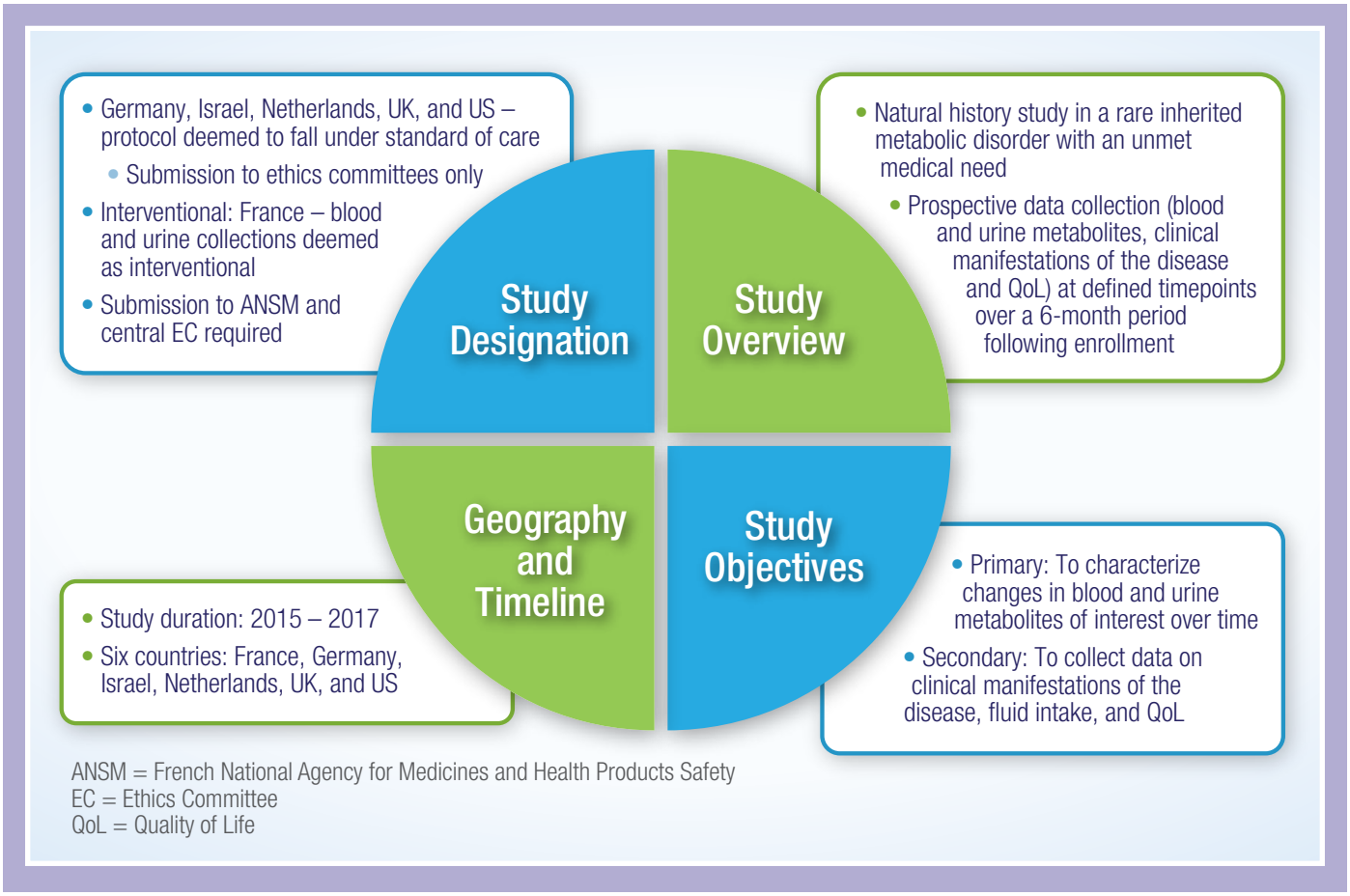


Figure 4. Case Study: Natural History Study in a Rare Disease Indication



Operational Approach to Natural History Studies with Genetic Testing

Case study

Figure 4 presents the case of a multi-country natural history study including genetic testing and how the different countries classified each study, together with the consequences in terms of regulatory process and ethics submission. This example shows the variability in study classification across geographies and within member states of the European Union (EU). Significant differences can be seen in certain geographies, particularly in France where we see non-routine biological sample collection for prospective research defining the study as interventional.

Practical implications

In practical terms, the lack of harmonized regulations regarding biomarker and genetic sampling, particularly in the context of natural history studies, means that product developers and researchers need to tread cautiously when planning research and carefully assess the regulatory landscape on a case-by-case, country-by-country basis to determine how to proceed. For example, regulatory requirements in France for studies involving biomarker genetic sample collection are clear, and both Ethics Committee (EC) and Regulatory Authority (RA) approval are required, whereas in other countries where regulatory requirements for genetic testing are less defined and therefore open to interpretation, advice may need to be sought from regulatory bodies beforehand in order to ensure the correct pathway is taken to secure approval.

Despite the current lack of guidance, genetic testing implies some responsibilities for the study sponsor and potential consequences for the patient that need to be considered. The ethical and patient care implications of genetic testing might expand beyond the scope of the proposed research. For example, if the patient is determined to have a confirmed or suspected pathogenic mutation:

- Should the patient be informed? Who should inform, counsel, and manage the patient?
- What happens if the significance of the finding is unclear at that time, or the significance only becomes clear many years after the patient was tested?
- Is there an obligation to provide additional patient monitoring or management because of a genetic testing result? Who decides what is appropriate for each patient?
- Is there an obligation to inform and/or test family members for the mutation (e.g., cascade screening)?

Conclusion

The emergence of new therapies focusing on rare diseases and targeted oncology indications leads to new needs in terms of real-world evidence generation, with the development of a new kind of natural history study that includes biomarker testing. These new needs challenge the regulatory framework that was initially shaped by clinical trials and traditional non-interventional studies, and this new situation translates into a diverse and moving regulatory environment for this new type of study. A timely and integrated multidisciplinary approach based on consistent strategic (why), scientific (what), and operational (how) considerations allows for anticipation of challenges and planning of preparatory steps for successful implementation of such studies. ■

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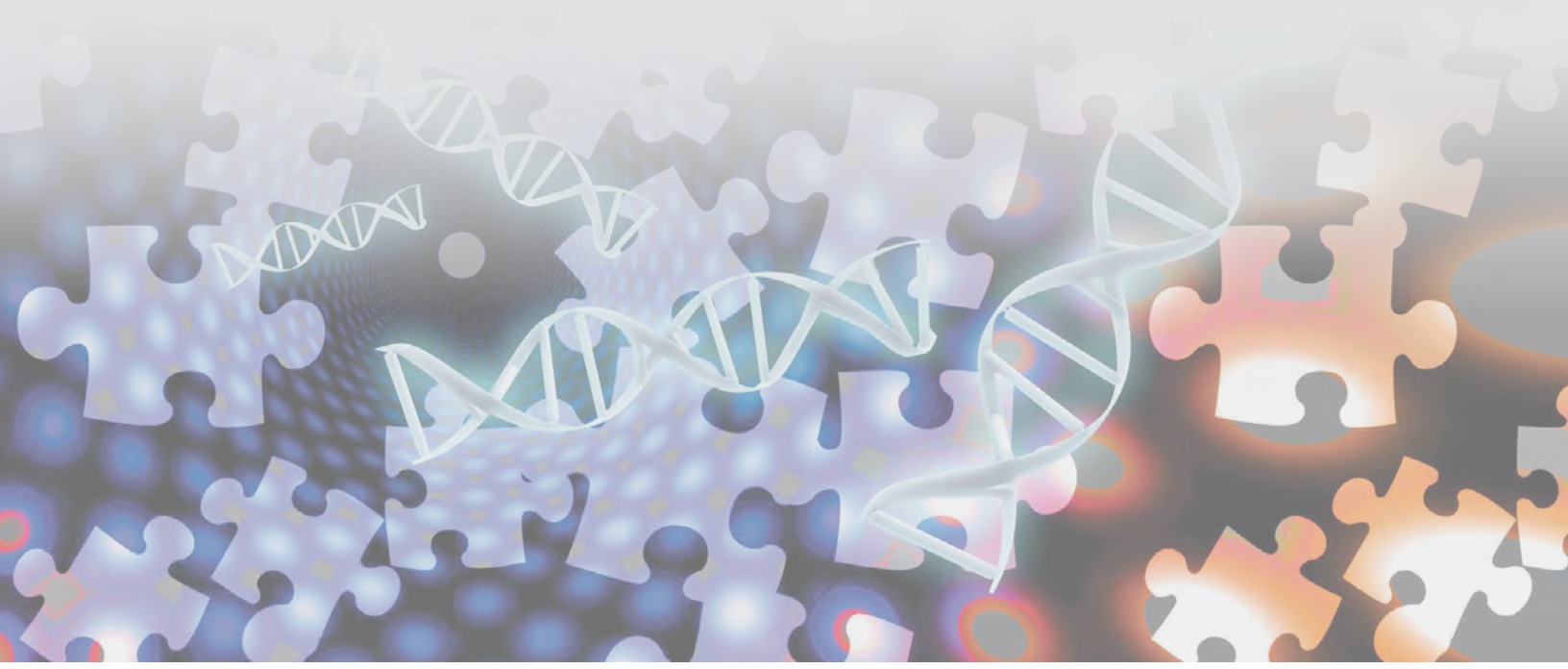

Evidence Requirements for Orphan Drugs from a Payer Perspective

How Can Early Scientific Advice Help?

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This issue of *The Evidence Forum* includes discussions on a variety of methodologies that can be used to understand, characterize, and document unmet need and product value in rare diseases. One question that comes to mind is, "Do we need all this? If a disease is rare enough, and severe enough, doesn't the unmet need speak for itself?" If only it were so easy! As anyone who has worked in rare diseases in the past decade can attest, the "glory days" of easy market access for orphan drugs – if they ever existed – are over.

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

Karen Sandman

Leigh Ann White

The balance between the desire to provide equitable treatment to patients with rare diseases and the need to contain healthcare spending can lead to unique challenges in demonstrating the value of orphan drugs. The core principles of market access apply, regardless of the disease: the manufacturer needs to make a clear case for burden of illness, unmet need, clinical efficacy and safety, comparative effectiveness, patient-relevant outcomes, and economic value. In the case of orphan drugs, however, evidence may be scant, or it may be necessary to provide additional context for the available evidence.

In general, teams who are preparing to launch drugs in orphan indications have strong awareness of the level of evidence needed to support their product's value proposition, but for any number of reasons their evidence package often falls short in one or two key areas. The two main reasons tend to be that:

- The market access and HEOR teams are not involved early enough in the process – often because the product was acquired close to launch
- Those responsible for the pivotal trial design are unaware or skeptical of the need for payer-relevant endpoints, such as healthcare resource utilization and a validated, disease-specific measure of health-related quality of life

One way to preemptively address these issues is to seek Early Scientific Advice, in which manufacturers can consult with regulators and health technology assessment (HTA) bodies regarding the types of clinical and HEOR evidence that would be necessary and sufficient to support regulatory approval and market access (See Table 1). Unlike a purely regulatory consultation, Early Scientific Advice engages with market access experts to obtain input on the types of evidence that would be most supportive during the HTA process. Early Scientific Advice, which is non-binding, can come from a single HTA authority, such as the G-BA (the Federal Joint Committee) in Germany or NICE (National Institute for Health and Care Excellence) in the UK, or it may include multiple HTA bodies, in the context of EUnetHTA Multi-HTA Early Dialogues or EUnetHTA/European Medicines Agency (EMA) Parallel Consultation.

A manufacturer should plan ahead to engage in Early Scientific Advice as it may take about six months to prepare for the process, which should occur during Phase II. Ideally, there should be time for clinical development and market access teams to consider how to apply the advice to the Phase III trial design and to additional studies to address payer evidence gaps.

Instead of having to differentiate a product in a crowded primary care market, often with generic competition, manufacturers of orphan drugs are faced with the challenge of finding difficult-to-obtain evidence, which requires a good deal of planning and foresight. Ultimately, though, payers are looking for the same types of evidence regardless of how many patients are affected by the disease – does this product safely and effectively address an unmet medical need, and is its cost acceptable within the constraints on how we spend our healthcare funds? With Early Scientific Advice, the manufacturer has an opportunity to discuss with decision makers before finalizing the evidence generation plan, to ensure that the studies ask and answer the most relevant questions. ■

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Table 1. Key Questions Addressed in Early Scientific Advice … and How They Relate to Orphan Drugs

Study Population/Indication

- What will the patient population be in real-world practice? How will clinicians identify patients?
- How is the population defined in trials, and how might payers react when making coverage and reimbursement decisions?
- How might inclusion/exclusion criteria impact generalizability of results for payers?

How solid are your prevalence estimates?

- Manufacturers often state that the budget impact of an orphan drug will be low based on the very small target patient population.
- For this economic argument to be compelling, there must be strong confidence in prevalence estimates.
- For maximum credibility, it is advisable to use current, scientifically rigorous prevalence estimates, particularly when these estimates will support an economic analysis.

How do I know the target population is not going to creep up to higher levels, especially now with increased awareness and potentially more diagnostic testing?

- With increased disease awareness and the broader availability of genetic testing, there may be more patients genetically diagnosed with a rare disease, who would not have been diagnosed according to standard clinical criteria.
  - Payers may be concerned about the potential for the target population to expand to higher prevalence levels, with increasing budget impact.
  - It is critical to reinforce the commitment to appropriate use.
  - Prospective observational studies of patients with less severe phenotypes may help to establish the disease burden and better elucidate appropriate treatment for these patients.

Study Design

- Are the endpoints appropriate for both regulators and payers?
- Is the study of adequate duration? How important is long-term follow-up?
- Are the planned subgroup analyses sufficient for payers? Which must be powered, and which subgroup analyses should be planned but not powered?

The efficacy data are limited to one year. We need longer-term data to evaluate the benefits and risks of this treatment.

- Eager to bring an effective product to patients with limited treatment options, orphan drug manufacturers often submit relatively short-term data for regulatory approval.
- Extension studies and registries can provide the longer-term efficacy and safety data being sought.
- Long-term extension studies and registries should include payer-meaningful outcomes, such as resource utilization, patient-reported outcomes, and long-term safety.

There is no active comparator (or there is no comparator at all) in the registrational trial.

- Often in a rare disease, there is no acceptable active comparator, and when the unmet need is large, it may be considered unethical to conduct a placebo-controlled trial.
- An indirect treatment comparison may be useful in lieu of a head-to-head clinical trial, but this depends on the availability, quality, and relevance of published trials of other treatments.
- It is essential to be upfront and clear about appropriateness of the trial design for an orphan drug.
- Keep the message focused on efficacy benefits in a disease characterized by substantial burden and unmet need.

You are showing me efficacy based on an endpoint that I can't correlate to real life. Does this endpoint translate to increased survival? Decreased resource utilization? Pain reduction or improved quality of life?

- Orphan drugs may receive approval based on a biologically relevant, surrogate endpoint that is clearly correlated to the product's mechanism of action.
- The pivotal trial should be designed to capture outcomes that are meaningful from a clinical, humanistic, and economic point of view.
- If the pivotal trial has already been designed, and the endpoints do not cover all the relevant topics:
  - Can real-world evidence correlate the trials' primary endpoint with some more meaningful outcomes?
  - Would patient interviews or vignettes demonstrate the relevance of the surrogate endpoint?

Comparator/Standard of Care

- What is the standard of care from the HTA perspective?
- What would need to be shown to differentiate the product from the standard of care?

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

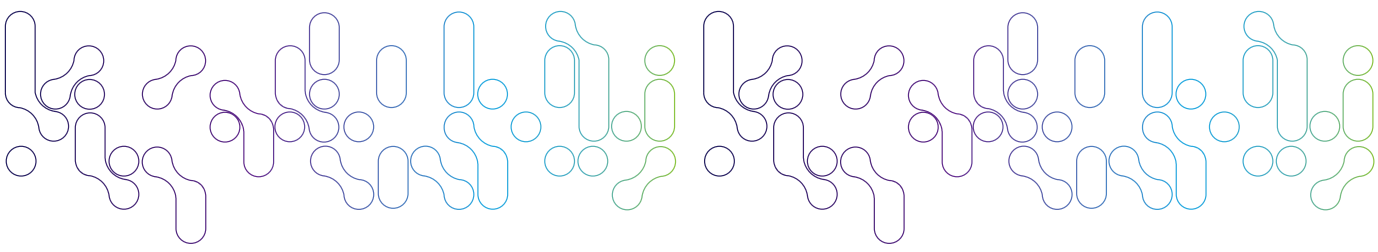
- For many rare diseases, standard of care has been defined by the lack of suitable treatment options, leading to the perception that patients do reasonably well without active treatment. It is necessary to establish the true clinical burden and unmet need, including consequences of untreated disease progression, in the rare disease.
- A careful and comprehensive review of the literature may provide sufficient evidence on disease progression.
- A detailed chart review or other type of real-world study can reveal the true clinical burden and unmet need in a rare disease.
- Disease simulation models can also be useful tools to correlate disease pathology with long-term clinical consequences.

Evidence Gaps

- What evidence not captured in trials may be needed for HTA?
- Is there a need for observational studies, registries, long-term extensions?
- Is the planned approach for collecting/using health economic data acceptable? What is missing?

The economic analysis is not sufficiently robust: the inputs of the model rely on assumptions that are inadequately justified (e.g., utility values, survival benefit, likely underestimate of costs, assumptions regarding the product alleviating the need for other standard supportive treatments).

- Ultimately, if there is a strong base of evidence relating to burden of illness, unmet need, clinical efficacy, safety, comparative effectiveness, and patient-relevant outcomes, then it should be possible to develop a robust and credible economic analysis of the treatment of an orphan disease.
  - There are places where all these types of evidence can fall short, especially in the case of orphan diseases, where literature may be sparse and available patient data may be limited.
  - By taking a proactive and thoughtful approach to building the evidence dossier for an orphan drug, it should be possible to support a compelling value proposition.



Can Early Collaboration between Multiple European Stakeholders Increase Access for Patients Living with Rare Diseases?

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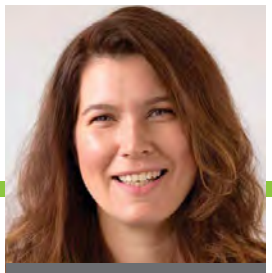
Almost 20 years ago the European Parliament adopted legislation in order to incentivise manufacturers to develop and market medicinal products to treat rare diseases.[1] Although this legislation stimulated research and development in the European Union (EU), access to these treatments remains inconsistent among EU Member States, which may in part be due to differences in assessment criteria between the various stakeholders.[2,3] There is often a gap between regulatory, health technology assessment (HTA), and payer requirements, which is further complicated by inconsistencies in value assessment between individual EU Member States.

Given the low patient numbers and the high unmet need for new treatments in rare diseases, it is crucial for manufacturers to develop an evidence package that meets the needs of all stakeholders – including regulators, HTA bodies, payers, and patients – to achieve access with certainty and speed across the EU. However, assessment and appraisal of medicinal products to treat rare diseases can be challenging in Europe given the differences in evidence requirements and assessment methods, which often results in different stakeholders reaching different conclusions on the access and reimbursement of a product.

Over the past several years we have seen an increase in collaboration between regulatory and HTA bodies as well as increased collaboration among country authorities. The ability for manufacturers to participate in integrated Early Scientific Advice (ESA) and collaborative multi-country HTA initiatives, such as the European Network for Health Technology Assessment (EUnetHTA), can help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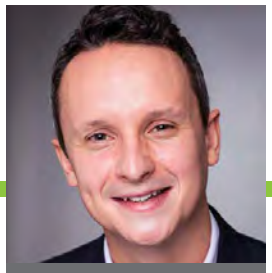

Matthew Bending

manufacturers of medicinal products for rare diseases optimise their product development and increase the likelihood of obtaining patient access across the EU.

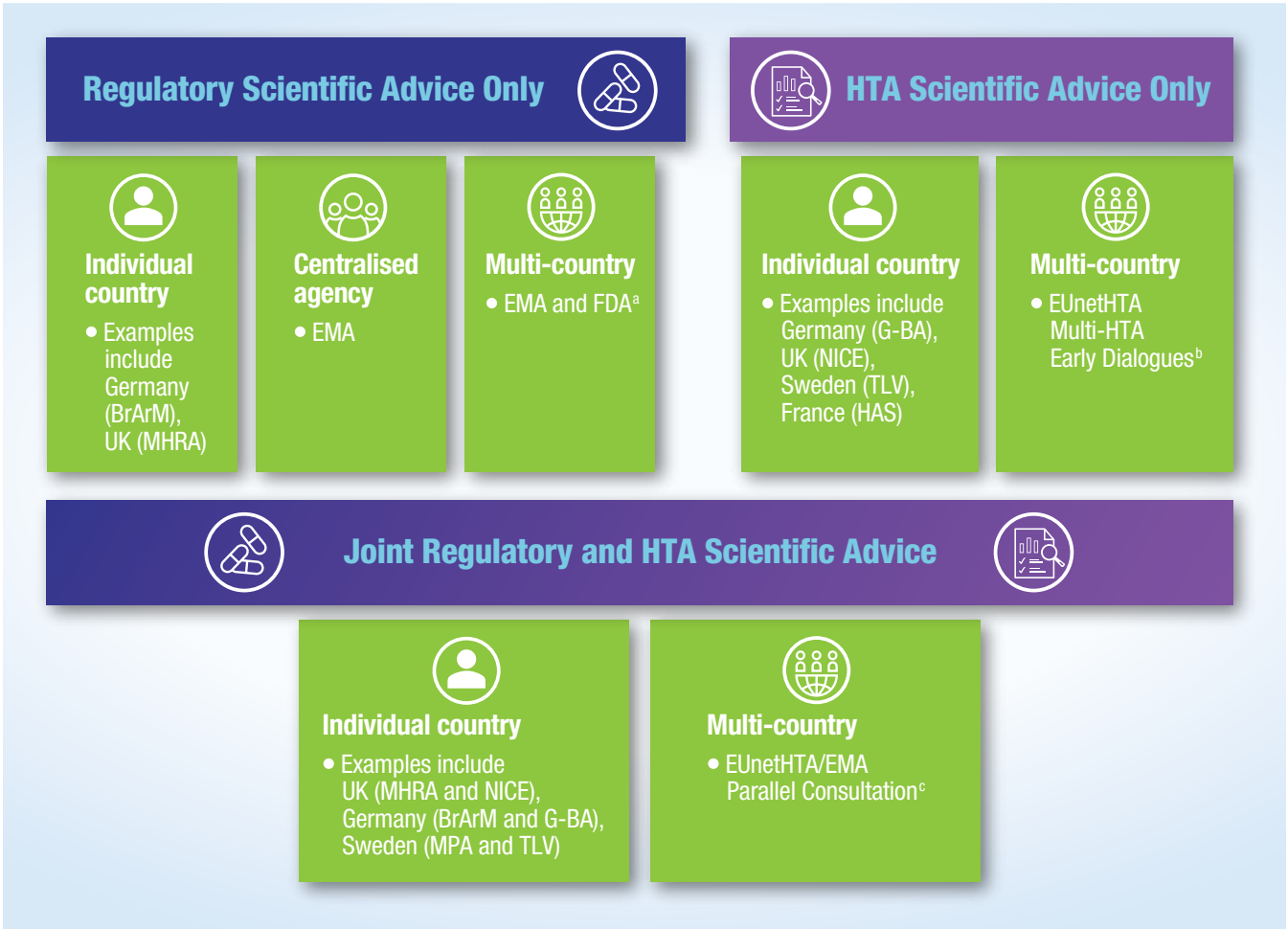
Integrated Early Scientific Advice in Europe

There are several types of ESA available to manufacturers in Europe including regulatory-only advice (either with country-level agencies or the European Medicines Agency [EMA]), HTA-only advice (either with individual country-level agencies or multi-country collaborations), as well as multi-stakeholder integrated joint scientific advice which involves both regulatory and HTA (See Figure 1).

Integrated joint ESA may be of particular utility in rare diseases since it provides manufacturers with an understanding of key evidence gaps and, importantly, allows them to explore how these gaps could be filled to meet both regulatory and HTA requirements.

The EMA/EUnetHTA parallel consultation brings together stakeholders from multiple countries, including both regulatory and HTA bodies. EMA/EUnetHTA parallel consultation includes two pathways – a consolidated pathway and an individual pathway.[4] The consolidated pathway guarantees the input of the EUnetHTA Early Dialogues Working Party (EDWP) which includes HTA representatives from France (HAS), Germany (GBA), England (NICE), Italy (AIFA with alternate RER), Hungary (NIPN), and a shared seat for the Netherlands/Belgium (ZIN/RIZIV-INAMI), plus up to three additional HTA bodies. EDWP members are guaranteed to take part in the consultation. Only certain products can be selected for the

Figure 1. Types of Early Scientific Advice Available in Europe



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b EUnetHTA. Procedure Description for EUnetHTA Multi-HTA Early Dialogues for Pharmaceuticals, 26 February 2018. Available at: https://www.eunethta.eu/wp-content/uploads/2018/03/Multi-HTA-Pharma-Procedure_180227.pdf. Accessed March 7, 2019

c EUnetHTA and the European Medicines Agency. Guidance for Parallel Consultation (EMA/410962/2017), 30 June 2017. Available at: https://www.eunethta.eu/wp-content/uploads/2018/03/Guidance-on-Parallel-Consultation.pdf. Accessed March 7, 2019

consolidated parallel consultation pathway due to resource constraints, and the individual parallel consultation pathway is offered as an alternative.

To be considered for the consolidated parallel consultation pathway, a product must meet all the following criteria:

1. Includes a new mode of action for the indication
2. Targets a life-threatening or chronically debilitating disease
3. Responds to unmet need (no treatment or only unsatisfactory treatment available)

Patient engagement has been recognised to be an integral part of the EMA/EUnetHTA parallel consultation process, and individual patient experts have been welcomed to participate in consultations to date. Patients have been identified through patient organisations under the EMA framework for interaction and are invited to join all meetings.[5] In addition, KOLs are invited to participate in the consolidated parallel consultation.

Obtaining scientific advice from both regulatory and HTA bodies across several countries in an integrated manner provides manufacturers with a strong rationale for clinical development plan decisions. However, there are often challenges to consider when seeking ESA, such as the intense and sometimes conflicting demands during product development, the need to gather internal cross-discipline alignment, and the risk of vastly different opinions from HTA bodies and regulators. It is important for manufacturers to identify the challenges early and seek support where necessary in order to maximise the potential of ESA.

Collaborative Multi-Country HTA Initiatives in Europe

One of the greatest challenges in rare diseases is the demonstration of clinical relative effectiveness, which is critical to HTA. Differences in HTA processes and methodologies can lead to differences in how clinical relative effectiveness is determined in assessments; collaboration by HTA bodies may decrease the disparity on how clinical relative effectiveness is both defined and assessed. EUnetHTA was set up to support collaboration between European HTA organisations and consists of a network of over 80 organisations in 30 European countries.[6] EUnetHTA has developed methodological frameworks for collaborative production and sharing of HTA information and also undertakes assessments. However, participation by EU Member States in EUnetHTA is voluntary and funding is short-term. This means clinical assessments of the same technologies are still being conducted in parallel across Member States and there is no guarantee for the continuation of these voluntary HTA collaborations in the long term. A 2018 EU HTA Directive (2018/0018) published January 2018 and adopted April 2018 aimed to address some of these shortcomings.[7] The Directive set out four pillars of work including joint clinical assessment (JCA) for all EMA approved pharmaceuticals. The JCA will focus on the comparative clinical assessment of the technology with clinical relative effectiveness a key domain. The JCA process will therefore require agreement from stakeholders on the centralised methods and assessment criteria used to determine clinical relative effectiveness.

The EU HTA Directive also aims to create synergies between the regulatory and HTA processes through mutual information sharing and better alignment of the timing between the proposed JCAs and the centralised marketing authorisation. Another pillar of work set out in the Directive is Joint Scientific Consultation (JSC), under which manufacturers can make a request for an early dialogue during the development phase of a product. These consultations can include only HTAs or EMA and HTAs in parallel. The aim of these consultations would be for manufacturers to seek advice on the data likely to be required for a potential future JCA. During the European Parliament's September 2018 meeting it was agreed the JSC, when addressing orphan medicinal products (i.e., treatments for rare diseases that have been granted orphan drug status by the EMA), has to ensure that any new approach should not result in unnecessary delays for the product's assessment compared to the current situation and should take into account the pragmatic approach undergone by EUnetHTA. In addition, it was agreed that a tailored clinical assessment pathway may be developed for orphan medicinal products due to the limited number of patients enrolled in clinical trials and/or the lack of a comparator.

The new EU HTA Directive has been welcomed by EURORDIS-Rare Diseases Europe, a non-governmental patient-driven alliance of more than 660 rare disease patient organisations across the 28 EU Member States, who stated that the Directive "introduces fairness, equity, high scientific standards and efficiency in the decision-making process" which is in the interest of people living with a rare disease and the wider patient community.[8] EURORDIS-Rare Diseases Europe has also welcomed strategies to establish synergies between the EMA and EU HTA bodies emphasising the importance of quality of life as a key domain in both regulatory and HTA decision making.[9]

Currently there remain uncertainties surrounding the EU HTA assessment methods and their definitions, how the comparators will be selected, and what will be the role of real-world evidence and patient-reported outcomes. Some clarity on the methods for JCA was provided at the European Parliament's September 2018 meeting, which highlighted the merit of EUnetHTA methods. During the meeting it was also agreed that the development of the rules of engagement for Joint EU HTA should consider the results of work already undertaken in the EUnetHTA Joint Actions, including methodological guidelines and evidence submission templates.

Outlook

The role the National Institute for Health and Clinical Excellence (NICE), which has been a leading participant in the EMA/EUnetHTA parallel consultation and EU HTA harmonisation initiatives, will play following the UK's exit of the EU remains unclear. However, on 6 February NICE announced that it will collaborate with the Canadian Agency for Drugs and Technology in Health (CADTH) to offer parallel scientific advice which demonstrates the agency's willingness to expand its partnerships with decision-making bodies beyond Europe.[10]

There are also examples of collaborations between EU Member States that extend beyond the clinical assessment and include pricing and reimbursement decisions. The Beneluxa Initiative comprises the Netherlands, Belgium, Luxembourg, Austria, and Ireland and aims to "ensure sustainable access to innovative medicine at affordable cost for our patients."[11] The initiative includes a collaborative approach to focus on evaluating high-cost orphan medicines and involves both joint HTA procedures and collaboration on price negotiations.

The aim of multi-stakeholder collaborations should be to streamline and clarify evidence requirements to increase transparency, consistency, and timeliness. The goal of any harmonisation initiative should be to increase the speed and breadth of access of new medicines for patients. Whether the convergence of clinical assessment makes the hurdle for access to medicines to treat rare diseases higher remains to be seen; however, it may provide a clearer signal of the evidence requirements needed to meet European stakeholder needs, thus decreasing the likelihood of unexpected missteps along the way. In rare diseases, where small patient populations and limited resources mean gathering evidence is a significant challenge, anything to smooth the path to patient access is welcome. ■

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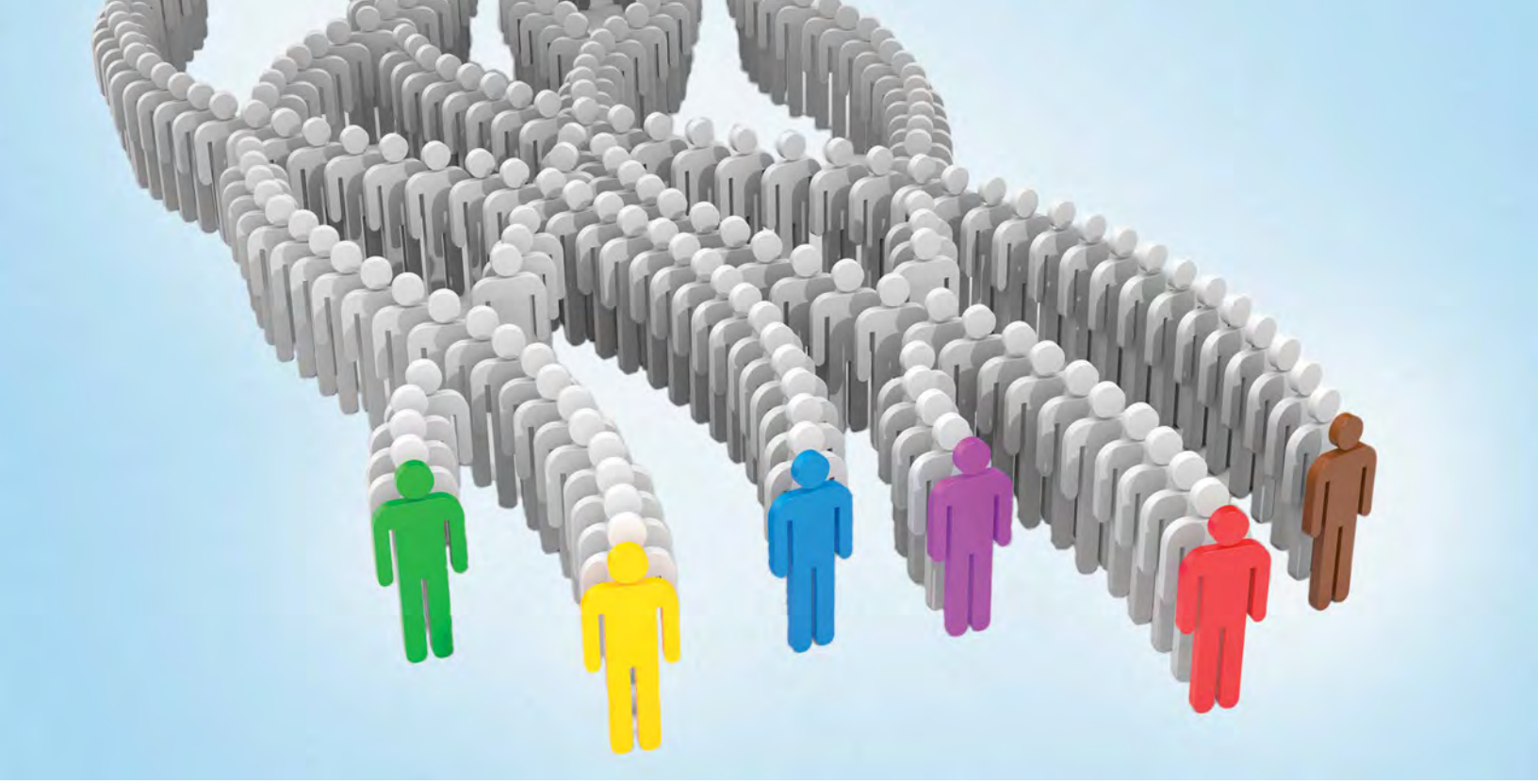

Clinical Outcome Assessment Selection for Rare Disease Trial Programs

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While there are a number of regulatory and industry guidance documents about the need for, and selection of, clinical outcome assessments (COAs), navigating through all of the information can be overwhelming. When you consider the nuances of a rare disease trial program, the overwhelming challenge can seem insurmountable. The aim of this article is to provide some baseline knowledge about the "why, who, what, and how" when it comes to clinical outcome assessments for rare disease trials.

Why include the patient perspective?

Patients are the recipients of the intervention being developed, but beyond that obvious reason, there is a legislative benefit for including patient perspectives. Under the 21st Century Cures Act (Title III, Subtitle A), there is a call to include patient experience data throughout the drug development process.[1] Sponsors have the opportunity to showcase the patient experience data, and there is a mandate for those data to be made public.

In rare disease product development, the patient perspective is particularly important because, often, not much is known about the disease experience. How the patient experiences the condition and the impacts of the condition are frequently heterogenous and not well understood. The US Food and Drug Administration (FDA) draft guidance, *Rare Diseases: Common Issues in Drug Development*,[2] concedes that, "medical and scientific knowledge, natural history data, and drug development experience" are often limited. The FDA is particularly interested in the patient experience and, as evidence of their interest, held a Public Workshop to outline their desire for such data.[3] The workshop illustrated avenues for

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engaging the FDA through patient advocacy and included case studies of how the patient's perspective can be introduced, and included, in the FDA's understanding of the patient populations.

The FDA has also produced guidance documents to assist Sponsors in rare disease drug development. The Pre-Investigational New Drug (IND) draft guidance specifically states Sponsors should be prepared to discuss the plan for including patient perspectives in their drug development program during the pre-IND meeting (line 281).[4] Furthermore, during the pre-IND meeting, Sponsors should also report about novel endpoints such as COAs (line 285).[4] COAs can be in the form of patient-reported, observer-reported, clinician-reported, or performance outcome measures.

Who should report the data?

The patient's perspective about their own experience should be reported directly by the patient. This may not be possible in rare disease as about 80% of the diseases hold a genetic component and nearly 75% of those affect children.[5] Other stakeholders such as a caregiver or patient advocate may be appropriate for reporting observations related to the patient.[6] Caregivers, such as a parent, can report observable signs, events, or behaviors. It should be noted that performance outcome assessments such as physical functioning assessments or cognitive testing may require specialty training and should be conducted by a healthcare professional.

What concepts from the patient perspective do we measure in a trial program?

When considering what concepts to measure in a trial program, begin by considering what is important, or meaningful, to the patient. The FDA advises, "signs and symptoms that are most important to patients" (line 151).[2] With a heterogeneous, rare population it can be a challenge to identify the most meaningful concepts.

Information about the concepts that may be measured can come from a literature review, desk research (e.g., Google), clinicians, and market research that may have been conducted by the Sponsor; there may also be an opportunity to partner with a patient advocacy group to gather qualitative data from the stakeholders themselves. These types of reports begin with concept elicitation about signs, symptoms, and impact. The report can also summarize risks and benefits of current treatment, adherence to medication regimen, economic burden, etc.

The disease experience information can be visually represented in a conceptual disease model (CDM), a tool that can be used to evaluate which aspects of the disease experience can be targeted for the trial program. Clinicians can be very helpful in giving insight into concepts that are clinically important. Consider focusing on common symptoms that can be directly reported by the patient, or observed by the patient caregiver, as well as concepts that will have time to change within the trial context. In rare diseases, it is often important to consider damage to the body that may be permanent and irreversible. Irreversible damage should not be captured as there would be no opportunity for improvement, even with successful intervention. The goal is to measure concepts that are important to patients, clinically relevant, and have the ability to react to a positive intervention.

How do we measure the patient perspective in the trial program?

The selection, or development, of a COA for a trial program should consider several factors.

- Who is reporting the data?
- How often are data being reported?
- What challenges with mobility or ability to report does the population have?
- What operational considerations exist (need for translations, mode of administration, and time to trial kick-off)?

In rare diseases, it is unlikely there will be a COA that will directly match the need for the trial program population. The Sponsor may wish to target very specific concepts and select individual COA measures. For example, an itch or sleep measure that can be reported by the patient or a physical function or cognitive performance assessment that would be evaluated by a clinician. The Sponsor can use the CDM to target areas to measure and then perform a review of existing COAs to identify measurement options. The goal is to see where the content you wish to measure overlaps with the content in existing COAs.

> The goal is to measure concepts that are important to patients, clinically relevant, and have the ability to react to a positive intervention.

It is possible that an existing COA measure has been developed and can be adapted to the rare disease. There is an example presented in this issue of *The Evidence Forum* by Drs. Murray and Bacci about the Evaluating Respiratory Symptoms (E-RS®) for idiopathic pulmonary fibrosis (IPF) (E-RS: IPF). The Sponsor may need to develop a new COA measure specific to their patient population. Considerations for rare disease can be made but the FDA guidance on PRO measures to support labeling claims should still be followed as closely as possible.[7]

While there can be challenges in the selection and inclusion of COAs in a rare disease trial program, hopefully the

information presented here has helped reiterate the value of including such measures. The patient's unique perspective is a critical aspect of evaluating efficacy. Often laboratory or imaging endpoints are used to evaluate efficacy of an intervention, but the patient is at the heart of the research and the question remains – how do we know if a change in those endpoints gives the patient a meaningful benefit? Supportive endpoints that rely on the patient or caregiver are vital. Sponsors should consider how the patient perspective is represented in the trial endpoints. If there is a question about what to include, the answer may be as easy as asking the expert – the patient! ■

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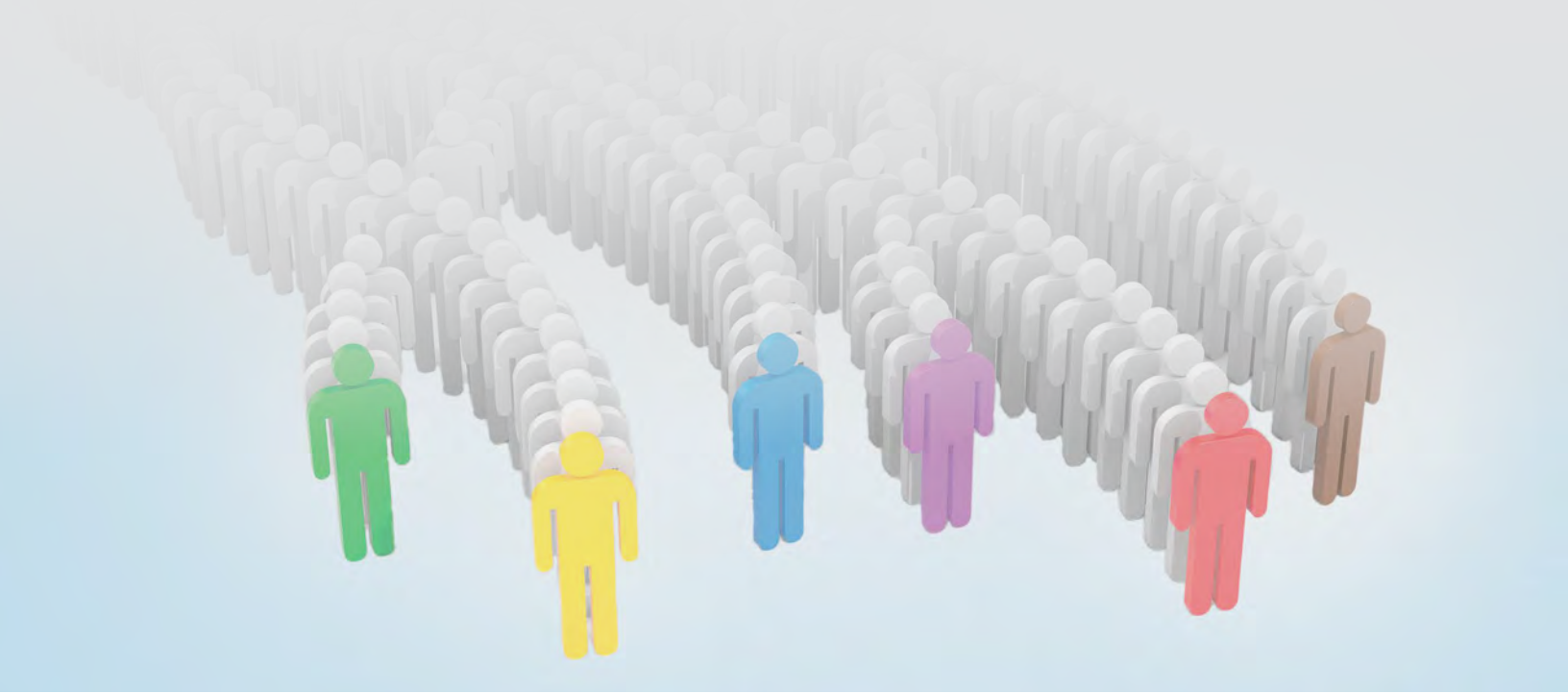

Adapting an Existing Instrument for a Rare Disease
A Valuable Resource within Your Reach

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Developing clinical outcome assessment (COA) tools specific to rare diseases can be extremely challenging due to a variety of factors, including: small numbers of patients in the target indication to participate in the tool development process; heterogeneity in the disease presentation; course and response to treatment; incomplete natural history of the disease; impact on vulnerable populations; the potential association with progressive cognitive and functional impairment, and/or lack of established clinical endpoints or biomarkers.[1,2] Taking these challenges into account, in the US Food and Drug Administration's (FDA) recent draft guidance on rare diseases, *Rare Diseases: Common Issues in Drug Development Guidance for Industry*, the "FDA advises sponsors to consider using or modifying existing assessment measures for the disease under study because evaluating novel measures is time consuming, with potential unexpected outcomes, and evaluations initiated late in the process could delay drug development. At meetings with FDA, sponsors should discuss the availability and modification of existing clinical outcome assessments" [p. 12, lines 457-462].[2] The FDA has previously published a Roadmap to Patient-Focused Outcome Measurement in Clinical Trials, which provides guidance on the steps for COA selection or development, including three key steps: 1) understanding the disease or condition; 2) conceptualizing treatment benefit; and, 3) selecting/developing the outcome measure.[3] However, it can be challenging to follow this framework within a rare disease indication. Thus, the ISPOR Rare Disease Clinical Outcomes Assessment Task Force has provided guidance on addressing the challenges to COA development within the FDA Roadmap framework, including these recommendations:

1. Use multiple sources of information including clinical experts, patients, and/or caregivers to inform the natural history of the disease
2. Focus on measuring common symptoms across patient subgroups, identifying short-term outcomes, and using multiple types of COAs to measure similar constructs
3. Adapt existing COA measures that include symptoms of importance to the rare disease under study[1]

To illustrate how an existing tool can be modified and adapted for use in a rare disease population, in line with FDA expectations of COA development, the focus of this article will summarize the adaption of the Evaluating Respiratory Symptoms (E-RS®) for COPD (E-RS: COPD) for


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use with patients with idiopathic pulmonary fibrosis (IPF). The E-RS: COPD scale is a derivative instrument of the EXAcerbations of Chronic obstructive pulmonary disease Tool (EXACT®) used to measure the effect of treatment on the severity of respiratory symptoms in stable COPD.[4,5] The instrument uses the 11 respiratory symptoms from the EXACT, including breathlessness, cough, sputum, chest congestion, chest discomfort, and chest tightness. In line with guidelines for PRO instrument development and regulatory expectations, development of the E-RS: COPD included concept elicitation interviews with COPD patients with and without a history of exacerbation, as well as extensive psychometric testing in both a natural history study and clinical trial programs.[4,6] In addition, experts in pulmonary medicine, clinical research, instrument development, and drug development regulators reviewed and evaluated results throughout the development process. Confirmatory factor analysis conducted during psychometric evaluations of the instrument supported a second-order model with a general factor, representing respiratory symptom severity overall (RS-Total), and three subscales representing the three key respiratory symptoms of COPD: RS-Breathlessness, RS-Cough and Sputum, and RS-Chest Symptoms. E-RS: COPD scores were designed to serve as primary, secondary, or exploratory efficacy endpoints in clinical trials evaluating interventions to reduce the severity of respiratory symptoms of stable COPD. Both the FDA and European Medicines Agency (EMA) have published qualification statements on the E-RS: COPD.[7,8] In addition, the E-RS: COPD has been incorporated into three labeling claims in Europe, supporting the qualitative and quantitative rigor of its development in line with regulatory expectations for use in COPD.

Combined with the developmental robustness of the tool, the symptoms included in the E-RS: COPD (breathlessness, cough, sputum, and chest congestion) are not unique to COPD. This makes the E-RS a good candidate for potential adaptation to other respiratory disease areas, including rare diseases. One such rare disease with a similar impact on respiratory functioning is idiopathic pulmonary fibrosis. IPF is a rare, progressive, and ultimately fatal pulmonary disease of unknown etiology with symptoms that can have a profound impact on patients' health-related quality of life (HRQoL). The natural disease course varies; some patients experience a rapid decline in pulmonary function, others report a steady decline over a few years, and some experience stable disease interspersed with acute exacerbations.[9] Increased breathlessness and cough are associated with disease progression, contributing to declines in physical functioning and HRQoL.[10,11] No disease-specific patient diaries for evaluating respiratory symptoms in IPF had been developed, therefore, the E-RS: COPD tool was selected for potential adaptation.

To adapt the E-RS: COPD for use in the IPF patient population, a 2-phase qualitative and quantitative study was conducted. In Phase 1, a cross-sectional qualitative study was performed to assess and document the content validity of the E-RS: IPF; i.e., the extent to which the E-RS: COPD items adequately and accurately reflect the respiratory symptoms of IPF patients.[12] Semi-structured telephone interviews were conducted with 30 adults with IPF using a combination of elicitation and cognitive interviewing techniques. The study assessed the extent to which IPF subjects would describe their respiratory symptoms differently or discuss any new respiratory symptoms not previously identified by COPD patients, as well as patient understanding of the items comprising the E-RS: COPD.[12]

> With so many instruments already developed and validated in more common diseases ... there is a rich source of data just waiting to be tapped.

Results of this qualitative research showed four categories of respiratory symptoms that IPF patients experience: breathlessness, cough, sputum, and chest symptoms. Breathlessness and cough were the most frequently reported symptoms. Respiratory symptoms experienced by participants in this sample were mapped to the items in the E-RS: COPD. All respiratory symptoms covered by the E-RS: COPD were endorsed by ≥30% of the IPF patients. Patients' descriptions of their respiratory symptoms were compared with the phrasing of E-RS: COPD questions and response options to determine if the wording of the items was appropriate for IPF patents. Overall, this study indicated the item content of the E-RS: COPD was appropriate for evaluating respiratory symptoms in IPF patients, and that these patients understood the content and structure of the items, thus supporting their content validity in IPF patients. No modifications to the instrument were made following these interviews.

In Phase 2, data from a Phase IIb clinical study in mild to moderate IPF patients (Parker et al. 2018[13]) was used to evaluate the performance characteristics of the instrument, including the factor structure. Exploratory factor analysis demonstrated that a four-factor solution, indicating four respiratory symptom subscales (IPF-Breathlessness, IPF-Cough, IPF-Sputum, and IPF-Chest Symptoms), best represented the data and no overall total score was appropriate. This finding indicates the only modification of the E-RS: COPD for use in IPF patients, as the E-RS: COPD is comprised of three factors and an overarching total score. Using this scaling structure, instrument reliability, validity, and responsiveness to change over time were assessed. These analyses indicated that the E-RS: IPF is a valid, reliable, and sensitive measure, although additional research is needed to confirm these findings in a separate patient population. Based on the results of this study, the E-RS: IPF may be a useful instrument for evaluating respiratory symptoms of IPF. This instrument was successfully adapted for use in a rare disease population, avoiding potentially significant challenges if an entirely new instrument was developed.

Roadmap to Patient-Focused Outcome Measurement in Clinical Trials - Application to Rare Disease Research and Idiopathic Pulmonary Fibrosis

1. Understanding the Disease or Condition	2. Conceptualizing Treatment Benefit	3. Selecting/Developing Outcome Measure
• Targeted literature searches and interviews with key opinion leaders (KOLs) were used to characterize patient natural history • Concept elicitation with IPF patients on respiratory symptom experience	Phase II multi-center, multi-national, randomized controlled study[13]	Respiratory Function • percent predicted forced vital capacity (FVC) Respiratory Symptoms • E-RS: IPF

Rare diseases present unique challenges in clinical trial design and in selection of COAs that can support claims in medical product labeling. Although guidance exists on suggestions for addressing these challenges, there is no "one-fit" solution to COA selection in a rare disease. Adapting existing instruments for use in rare diseases is one possible solution to the many challenges encountered in the development of rare disease treatments. Any advantage that can help simplify the process, efficiently utilize sparse and valuable resources, and potentially provide faster access to these specialized treatments that can help increase quality and length of life is worth investigating. With so many instruments already developed and validated in more common diseases that may include items relevant to other disease areas or populations, there is a rich source of data just waiting to be tapped. This article illustrates how an existing measure was modified for use in a rare disease population. More information on the EXACT, E-RS: COPD, and E-RS: IPF can be found at www.exactproinitiative.com. ■

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How Social Media Can Be Used to Understand What Matters to People with Rare Diseases

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Rare Diseases, Drug Development, Decision-Making, and the Patient Perspective

Rare diseases pose several challenges to the drug-development process. Since patients who suffer from rare diseases are infrequent and geographically dispersed, important medical and clinical information is often highly limited and difficult to locate. Furthermore, for many rare diseases there is not a high level of awareness among the medical community in general, and that can lead to misdiagnoses, extended pathways to correct diagnoses, and a lack of appropriate medical codes with which to identify the patients correctly. All these factors conspire to make it more difficult to understand the natural history, epidemiology, and progression of diseases that affect small and often highly diverse patient populations.

Understanding the patterns of healthcare, burden, and unmet needs of rare disease patients is equally difficult and frequently an almost impossible task. The challenge of identifying rare disease patients also makes it more difficult to conduct studies aimed at discovering their perspectives and needs. In recent years there has been a profound shift to a more patient-centric, drug-development process to ensure the patient voice is incorporated across all stages. This is particularly true for rare diseases, where incorporating the patient voice into orphan drug development is a priority.

In January 2019, the US Food and Drug Administration (FDA) published a revised draft guidance on rare and orphan drug development. The guidance encourages researchers to involve patients, caregivers, and advocates, having them provide input on their experiences, perspectives, and priorities related to potential endpoints used during the drug-development process and regulatory review.[1] The guidance also encourages the use of social media as a means to represent the perspective of the patients. Additionally, an increasing number of manufacturers are involving patient representatives in early trial design to understand whether trial protocols are acceptable from the patient perspective.[2]

The Increase in Use of Healthcare-Specific Social Media Platforms

Due to the low prevalence of rare conditions, patients and caregivers are geographically dispersed and may feel isolated, finding it difficult to speak with other patients and specialists about their condition. The need to connect and find support, especially across rare disease

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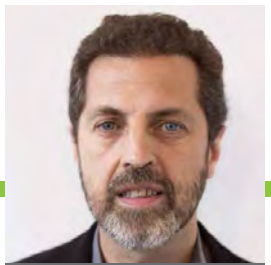


Andrew Cox

communities, has led to an increasing number of patients and caregivers turning to social media platforms for valuable insights on their disease.[3] Available healthcare-specific platforms include social networks that focus on rare disease communities, such as RareConnect,[4] created by EURORDIS[5]; rare disease discussion groups supported by closed-access online communities, such as Inspire[6] and Smart Patients[7]; Facebook groups; and, publicly accessible, disease-specific discussion boards. In these platforms, patients can share experiences and important information and offer support and advice. Patients frequently use these sites to share their entire experience with the disease, including side effects, treatments received, pre-diagnosis history, and outcomes. Some forums have posts dated from a decade ago or longer. This information is an important window into the perspective of patients with rare diseases, and in many cases, this is the only way to learn about patient experience.

Researchers have recognized the potential of these social media platforms in aiding orphan drug research and development. In a recent study[8] for a very rare paediatric condition, researchers recruited and surveyed the largest reported contemporary cohort of 671 people born with a single functional ventricle in their hearts by using Facebook, Twitter, and other social media platforms. Existing historical conversations on healthcare-specific social media can be used to support a wide range of research questions (See Figure 1).

How Can Healthcare-Specific Social Media Help?

Our experience shows that traditional approaches to evidence generation for many rare diseases rapidly reach a dead end due to a lack of appropriate medical codes and data sources, and the difficulty in reaching patients. To remedy this, creative approaches need to be adopted. With limited quantitative data available in health databases, contextual information gained through social media sources should be considered. Analysis of social media for rare diseases can provide a cost-effective means of illuminating the unmet needs, disease burden, opinions, treatments, side effects, and potential misdiagnoses of patients. Such information can also be used to better design patient questionnaires and patient preference studies.

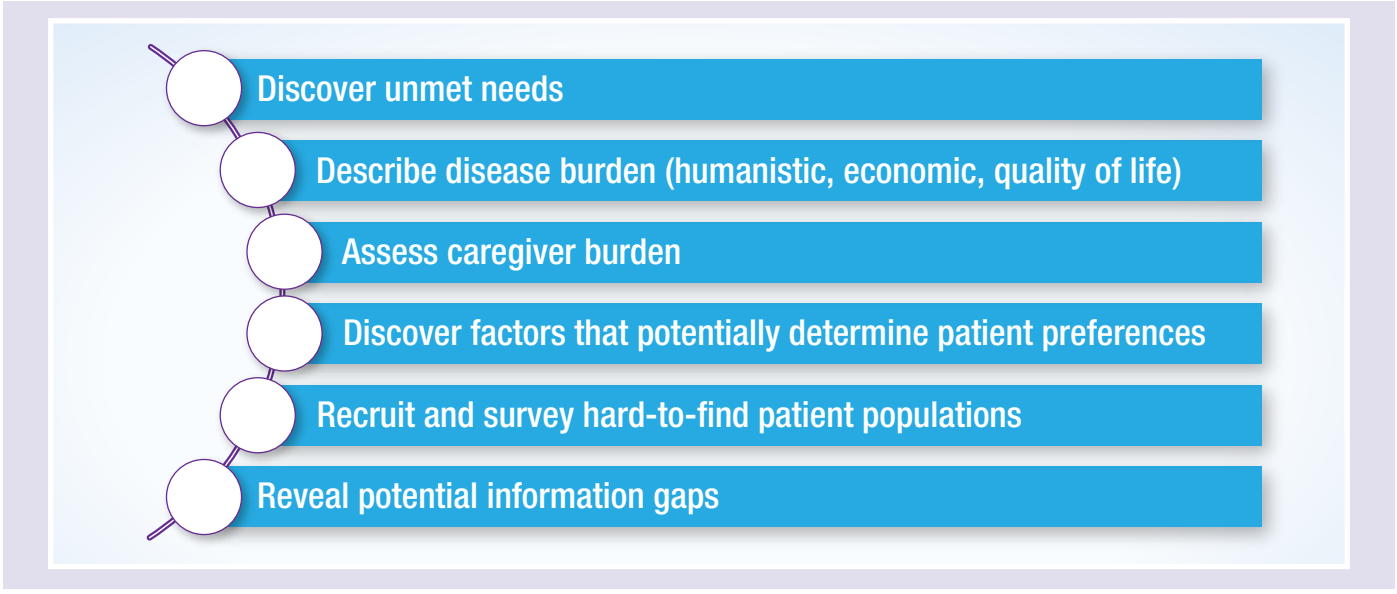
Another way social media forums can be used to better understand the patient perspective is to rely on the close-knit and connected nature of the rare disease community to participate in an online patient questionnaire study. Providing a secure patient questionnaire through social media allows patients in the community to share the link, creating a kind of snowball recruitment that can be highly effective.[8]

How Does the Use of Social Media Compare with the Patient Survey Approach?

Previous studies have compared the use of patient social media forums with the more traditional patient survey approach as a source of data for qualitative research aimed at capturing the patient experience.[9,10] The two studies referenced as examples both found that searching social media to capture patients' perspectives on the impacts of a disease is a feasible and fruitful approach. Social media searches may be useful as a preliminary step in research (e.g., for informing the development of discussion guides), and for supplementing the results of traditional qualitative approaches. The studies found both approaches highlighted common themes, with substantial overlap in the results; unique information was gathered in each approach, suggesting that they may be complementary.

A distinct advantage of social media is its shorter timeline; patient survey studies may take several months to complete and may lack the number of rare disease patients to allow saturation of important concepts to be reached. Studies based on social media can often incorporate many more

Figure 1. Potential Uses of Social Media Data in Rare Diseases



patients than can be reached in a survey and do not require a complex recruitment and interview process. One area of uncertainty for social media is the extent of potential bias in using this data source. While the potential biases in questionnaire-based studies are well documented[11] (one study catalogued 48 potential bias types), the use of social media as a qualitative data source is relatively new and the potential for bias is still being explored. However, social media studies can draw on larger sample sizes, which helps ensure that all common concepts are captured (saturation). Social media posts are unsolicited and not responses to specific questions, making them less prone to bias types introduced by the structure and design, as well as the interviewers, in a more traditional questionnaire-based study. Combining both study types would be the best approach to ensure more reliable and more in-depth insights into patient perspective.

Case Studies: Using Social Media to Understand Patient Experience of Acute Myeloid Leukaemia

Myelodysplastic syndromes (MDS) constitute a rare group of hematopoietic stem-cell disorders[12] that predominantly affect elderly patients.[13] According to a systematic literature review published in 2016, the global prevalence of MDS ranged from 0.22-13.2 per 100,000 people across all ages, genders, and ethnicities.[12] However, the actual prevalence of MDS is hard to estimate due to underreporting of MDS in cancer registries, and under-diagnosis of MDS in older patients[14] with cytopenias, particularly anaemias due to MDS.

Approximately one in three patients with MDS can rapidly progress to a life-threatening failure of bone marrow or develop acute myeloid leukaemia (AML).[15] The American Cancer Society estimates there will be 21,450 new cases of AML in the US in 2019, mostly in adults,[16] accounting for 1% of all new cases of cancer. Despite advancements in the treatment of hematologic malignancies (with the development of effective targeted and immune therapies), the survival rate of patients with AML is poor. Based on data from the Surveillance, Epidemiology, and End Results program (SEER) 2008-2014, the five-year relative survival rate in patients with AML was 27.4%.[17] Standard treatment approaches in MDS/AML largely depend on MDS risk and other prognostic factors, including patients' age and comorbidities, and patients' goals. More aggressive forms of therapy, such as stem-cell transplantations (SCT) and chemotherapy, are usually reserved for younger and fit patients who are at high risk. For elderly or frail patients who are ineligible for chemotherapy or SCT, supportive care is essential for improving quality of life.[18] Given the poor survival rate and significant unmet needs among patients who are ineligible for chemotherapy, it is necessary to understand and incorporate patient and caregiver perspectives and priorities into the development of an optimal care plan.

While traditional research approaches for reaching out to rare disease populations involve surveying patients recruited through disease registries or patient-advocacy groups, social media can offer a different avenue to accessing hard-to-find patient populations.

A growing number of studies have used social media sources to help understand the experiences, burden, preferences, and unmet need for rare disease communities. Kusumgar et al. examined around 7,000 posts from AML patients and caregivers, and the study found that 20 percent of posters were older than 65 years of age, which was somewhat surprisingly high given that social media are more popular in younger ages. Sixty percent of the discussion was conducted by caregivers, who assumed more social media responsibilities when patients relapsed or declined physically.[19] This shows that even if patients are unable to participate in social media, their experiences can still be represented by caregivers.

The study also found that patients and caregivers used social media to seek disease information, emotional support, to set treatment and recovery expectations, as well as to compare their experiences with others. The study also suggested a lack of practical patient-focused education and support via online and offline venues.

Two recent studies also utilized social media forum postings to understand the patient experience of AML and MDS.[20,21] These studies used 1,443 posts from 220 AML patients to explore the unmet needs and perspectives around treatment choices for those patients who were ineligible for intensive chemotherapy. Research found that the patients encountered a lack of information about treatments, and

Strengths and Caveats of Utilizing Social Media in Rare Disease Research

STRENGTHS	CAVEATS
✓ Can potentially access hard-to-find rare disease populations through online communities	➤ Patient privacy needs to be protected by de-identifying social media profiles
✓ Can get information on sensitive or difficult topics, such as perspectives in end-of-life decisions	➤ Representativeness of the data cannot always be assured
✓ Views are unsolicited and not subject to response bias that may occur in surveys/interviews	➤ May still suffer from small sample sizes
✓ Generates insights in a quick and cost-effective manner (average study duration 8-12 weeks)	

the condition in general. The studies concluded that clinicians need to ensure these topics are discussed and delivered in a manner that can help patients make more effective treatment decisions. Furthermore, a greater understanding of AML and its symptoms is required to potentially allow for earlier diagnosis.

Summary

Studying healthcare-specific social media forums can support research in rare diseases in many ways, such as helping to find and recruit patients for research studies. Analysing documented conversations can also help to incorporate patient and caregiver perspective into decision making. Social media offers insights comparable to patient surveys and has several advantages, such as reduced timelines to information, alternative perspectives, and analysis of experiences of higher numbers of patients. With much of the discussion and published material for rare diseases too often focused on the medical and scientific perspectives, analysis of social media data can serve the important aim of better representing the patient perspective. Analysis of these data can help to highlight important patient values and help the medical and scientific communities to better communicate with and understand the patients in their care. Furthermore, information gained in this way can help highlight unmet need, which can allow for better development and prioritizing of treatments. ■

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Registries in Rare Disease Research
Approaches to Optimize Success

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Advancements in gene therapy and transformative medicine have had a major impact on the development of treatments for rare diseases, resulting in a growing need for evidence of the safety, effectiveness, and value of these treatments in the real world. Opportunities to improve healthcare, clinical outcomes, and patient and caregiver quality of life are abundant, but for successful market access of novel treatments, robust – and frequently longitudinal – clinical and outcomes data from the usual care setting are necessary. A significant obstacle to collecting this data, however, is the low number of patients with the disease being studied. The US Food and Drug Administration (FDA) classifies a rare disease as any disease or condition affecting less than 200,000 patients in the US.[1] Hence, the identification and long-term engagement and retention of these patients is a primary challenge.

Registries can be an incredibly useful tool in gathering data on patient usual care, current treatment landscape(s), and long-term clinical outcomes, as well as other uses noted by recent FDA guidance,[2] to better understand the impact to the disease population and strategically plan for additional real-world patient research and treatment development. In observational, non-interventional registries, or disease-specific registries, used to gather real-world evidence, identifying, engaging, and enrolling as many of these rare disease patients as possible is vital to the success of the registry. One common challenge is convincing usual care physicians of the benefit of participation in these observational registries since no experimental drug is provided. In these cases, it is imperative to convey the importance of every real-world patient experience, particularly in rare diseases where there are so few patients available, and that every effort must be made to connect, involve, and embrace the opportunity to better understand the impact of treatments on patient outcomes outside of the clinical trial setting.

Success of a registry hinges largely on the study design, which can influence the operational aspects of the registry as well as patient engagement. The ability to operationalize the registry protocol is paramount – the best written


Linda Ross

protocol cannot be successful if it is not feasible within sites and with site staff. The protocol must be flexible to adhere to standard of care procedures; it must allow for variability in data collection as each treating clinician may conduct standard of care visits and document clinical information differently; and, lastly, it must not influence standard of care treatment for the patient – it must adhere to "the real-world" treatment paradigm. Although these key principles for real-world data collection must apply, there still exist inherent challenges to enrolling patients into registries, and even further challenges to enrolling patients into rare disease registries. How to best capture the patient data may depend on the protocol – disease-specific registries versus treatment-specific registries.

Treatment-Specific Registries

Treatment-specific registries are designed to enroll patients already receiving treatment, per physician intent. Therefore, all clinical data is associated to a specific product and focuses on treatment-specific clinical outcomes. The benefits of this study design are that it allows the audience to understand:

1. Focused demographics of patients diagnosed with the rare disease and prescribed the specific treatment
   - Is there a difference in the demographics of the patients receiving treatment and enrolled in the registry compared to the overall rare disease population as understood in published literature?
2. Clinical outcomes specific to the treatment
   - Are there clinical outcomes newly identified in the real world that were not identified during earlier clinical trials for the product?

Although registries would include all patients receiving treatment, there is a consideration that not all patients would consent to participate in the registry after receiving treatment as per usual care. Therefore, the population reflected in the treatment-specific registry would be a subset of the specific treatment population, which, of course, is associated with potential selection bias.

Key factors for increased treatment-specific registry engagement

Key patient recruitment and engagement initiatives that have proven to be successful in rare disease treatment-specific registries include:

1. Dual outreach and partnered communication by the sponsor and clinician to encourage patient participation
   - Developing direct-to-patient communications to highlight the value of participating in the registry
   - Coordinating sponsor partnership with advocacy group(s) and disseminating treatment-specific registry information via the advocacy group communication(s)
2. Sharing data results of the registry with the enrolled patient population
   - Sharing data results and helping the patient to better understand how his/her peers are responding to similar treatment helps patients feel engaged and empowered in managing their own care

Disease-Specific Registries

Disease-specific registries are designed to enroll "all-comers" of a rare disease into a registry. A patient with a diagnosis can be eligible for enrollment and ongoing observation within the registry without impacting standard of care treatment or schedules. The benefits of this study design are that it allows the audience to understand:

1. Demographics of patients impacted by the rare disease, regardless of treatment
   - Are there trends in race/ethnicity?
   - Is there a specific age range for diagnosis?
   - Are there socio-economic influences in rare disease diagnosis and treatment?
2. Current treatment landscape – insight into all of the treatment options patients with a specific rare disease have available to them
   - Are there specific treatment protocols/guidelines already established? Will new treatment approvals impact treatment protocols already in place?
   - Are there clinical outcomes associated with specific treatment regimens within the diseased population?
   - Are there complementary therapies that can enhance current treatments?

This also gives the sponsor flexibility in tracking their own product update versus other treatment options, all within the construct of the disease-specific registry.

Key factors for increased disease-specific registry engagement

Outreach to rare disease patient populations via a third-party can help ensure all patients feel included and encouraged to participate in the registry. Key initiatives that have proven successful include:

1. Developing direct-to-patient communications, with limited sponsor reference, to highlight the value of participating in the registry that is impartial to current treatment regimen, and emphasize the importance of the registry in promoting disease awareness and overall treatment improvement that is unbiased by currently approved product(s)
2. Coordinating with advocacy groups and disseminating further education about the rare disease, other/alternative treatment options, published data that may not be accessible to the general population, and promoting community events to engage patients in the advocacy activities

As noted in the recent FDA Guidance,[2] it is important to engage with key stakeholders, including patients, caregivers, and advocates, as their engagement can provide different perspectives and experiences to the registry. More patients are becoming empowered and involved with their own treatment regimen and educating themselves on treatment options.[3] Additionally, patients may look to patient advocacy initiatives[4] to further their own treatment regimen and better understand the treatment landscape. Therefore, it is imperative for rare disease registries to focus on operational efficiencies and successes experienced by other rare disease registries.

Importance of Patient Centricity

Recent implementation of rare disease registries has presented anecdotal evidence associated with geographical regions.

- **North America and Europe** – patients look for the opportunity to independently opt-in to clinical research, autonomous from their clinician
- **Latin American and Asia Pacific** – patients rely upon their clinician's recommendation to participate in clinical research

This trend may be due to several reasons, including cultural norms regarding clinical research; levels of exposure to observational, non-interventional registries in these regions; and, personal levels of comfort in disclosing medical information to an electronic database.

Outlined below are some key considerations that can be beneficial when identifying and approaching potential registry patients for either treatment-specific or disease-specific registry designs.

Create a Network/Community

- There has been an increase in patient advocacy, such as the National Organization for Rare Diseases (NORD) and other similar resources, and rare disease registries can find much success when partnering with patient and caregiver advocacy groups. This can help legitimize the research initiative, as well as provide a sense of comfort for the patient and caregiver in feeling that their peers are also included.
- Investment in key marketing and branding efforts can further this development of a "virtual community" and "network."

Share More Data

- Sharing data results of the registry with the enrolled patient population and helping patients to better understand how their peers are responding to similar treatment helps patients to feel engaged and empowered in managing their own care.

Utilize Technology

- As technology embeds itself more and more into our day-to-day activities, there has also been increased use of technology in successfully launching registries. Initial patient screening, encouragement of self-enrollment, reduced burden of data collection, and streamlined user interface for information sharing – these all have a benefit in further extending the engagement reach to rare disease patients.
- Third-party, database vendors with the ability to pre-screen patients based upon Electronic Medical Record (EMR) data and then "invite" patients, via an opt-in portal, have also helped to further the screening/enrollment outreach and improve registry data results.

Registries provide an abundance of real-world insight into rare diseases, the populations who are afflicted by them, and the newly approved therapies that treat them. The data gathered through these studies can help guide research objectives and direction, identify future real-world patient studies, and help build the foundation for strong value story development to help optimize the chance of market access. While there are inherent challenges in designing and operationalizing any registry, those designed for rare diseases present additional challenges in patient identification, engagement, and recruitment. Success comes with overcoming these challenges through a multi-faceted approach that uses proven best practices, innovative solutions, and evolving resources. ■

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More Evidence Needed for Orphan Drugs in Germany

A Hurdle for Access and an Opportunity for Real-World Evidence

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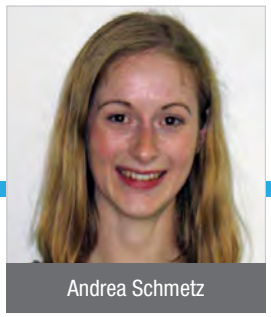
As a reaction to the recent drug safety incidences in Germany (including drugs contaminated with potentially carcinogenic substances, illegal drug imports, and incorrect drug dosing by a pharmacist), the German Ministry of Health introduced a draft "law for more safety in the supply of pharmaceuticals" (GSAV) in November 2018 (See Figure 1). The bill is still to be voted on in both chambers of the German Parliament and, if accepted, will come into effect 1 July 2019.

One of the main components of the draft law is the demand for **better evidence for orphan drugs and drugs with conditional approval** and a change to the **revenue threshold for orphan drugs**.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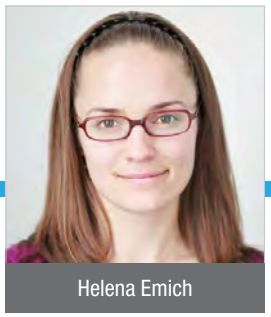
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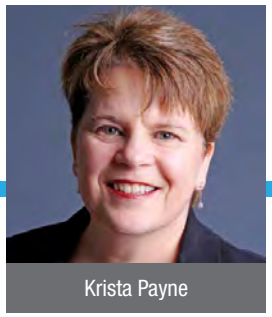
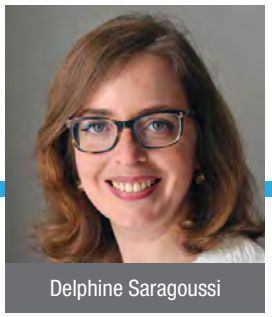

Krista Payne

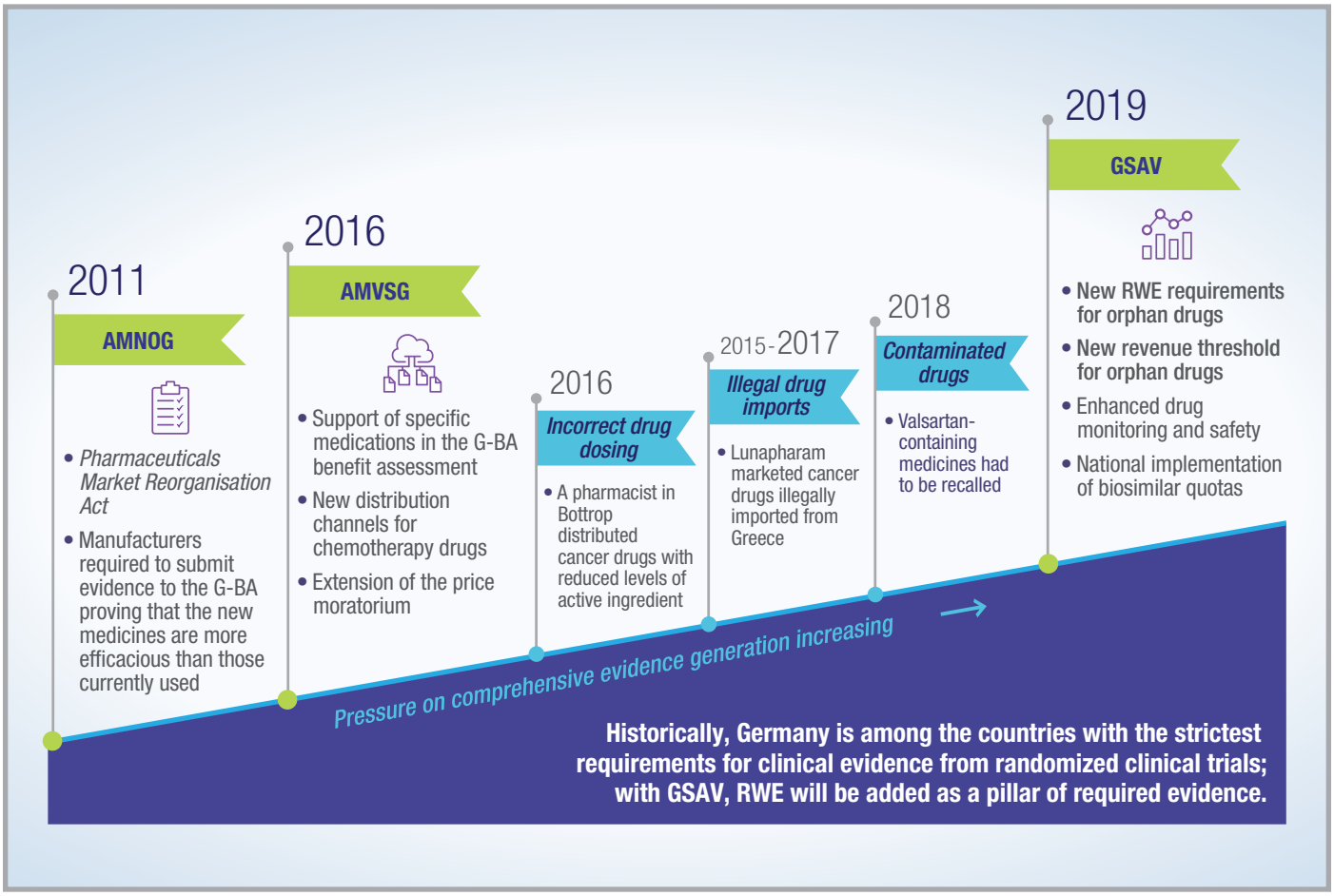

Delphine Saragoussi

In general, orphan drugs brought to market in Germany enjoy the advantage of an assumed benefit, meaning the worst potential outcome in health technology assessment (HTA) is a non-quantifiable benefit. However, traditionally, if the product's revenue in the retail market exceeds an annual turnover threshold of €50 million, the product then requires a full benefit assessment under AMNOG without the orphan medicine advantage of an assumed benefit. In this case, the manufacturer needs to provide additional evidence, likely against an active comparator. Beginning in July, all revenue from product sales – not only retail but also hospital, etc., – will go towards the €50 million threshold. This could affect several drugs and give the G-BA the legal means to reassess several orphan assets, closing an obvious accounting loophole.

In the light of recent concerns with safety and long-term efficacy of multiple orphan drugs, the Ministry of Health has also taken steps to increase evidence requirements for orphan drugs. The G-BA has already, within current means, tried to limit the long-term impact of insufficient data with additional restrictions, e.g., in the case of a treatment for primary biliary sclerosis assessed in 2017, where the G-BA demanded a re-evaluation with long-term data to be made available in 2023. Similarly, a treatment for spinal muscular atrophy (SMA) was also given restrictions mandating additional evidence, albeit the timeline is only until 2020 when the drug is due to be reassessed. The new GSAV law will expand the means to increase restrictions even more, as it specifies that the G-BA can demand **additional evidence for all assets with conditional approval** (given due to missing evidence) or for **orphan drugs** (where the evidence base is considered low). This additional data required should be collected as real-world evidence (RWE), the exact specifications to be outlined by the G-BA. The evidence will be reviewed at least yearly, making it technically possible for the G-BA to re-evaluate drugs on a yearly basis. Should the manufacturer fail to comply with the request for additional evidence or if the submitted evidence leads to a negative reassessment outcome, the German statutory health insurance system (GKV) will have the right to discount the price of the asset. Of note, a lack of evidence can lead to a price discount, however, favourable evidence cannot lead to a price increase due to the existing price moratorium, which is in force until the end of 2022.

The new regulation regarding additional evidence presents new opportunities to **incorporate real-world evidence,** which so far has not been looked upon as acceptable by the German HTA. Considering the impact of this data, any future evidence generated should be both comprehensive and high quality.

Figure 1. The Changing Legal Framework and Increasing Evidence Requirements in Germany



> Early engagement in strategic real-world evidence generation planning, in the context of these new opportunities for market access optimization, will be paramount…

It is possible that in the future this new rule could be expanded to all drugs assessed under AMNOG, Germany's law regarding the marketing of pharmaceutical products. This would offer manufacturers the ability to launch a new product earlier based on limited evidence and substantiating the evidence base with RWE data in the years after launch, as long as manufacturers are confident that the evidence produced will be able to support their needs. The RWE data generated in Germany (the largest market in Europe) could then potentially be used to support launches in other European markets as well. Along these lines, consideration should be given to whether there are potential synergies between post-authorisation safety studies requested by the European Medicines Agency (EMA) and RWE requested by Germany.

Real-world evidence methodologies include a diverse array of study types depending on the questions that need to be answered and the data needed to answer them appropriately. For example:

- **Early natural history studies** are used to characterize patient groups of interest and unmet medical need, and with the growing attention on rare diseases, there is a greater need to accurately define the profile, characteristics, and disease outcomes of target patient populations. (See "Natural History Studies in Rare Diseases and Genetic Biomarkers" by Bevan, Ringo, Fitzgerald, Kearney, and Saragoussi in this issue of *The Evidence Forum*.)
- **Burden of illness studies** evaluate patterns and costs of care and provide insight into the journey of rare disease patients, including the economic challenges, the emotional burden, and the effects on their quality of life. These data can be particularly revealing of those sufferings from rare diseases, where care options are limited and often difficult to access and the emotional burden can be overwhelming with little support from others with the same condition. Data from these studies can help provide a more complete and compelling value story for rare disease treatments.
- **Comparative effectiveness studies** help identify the value of a new treatment compared to existing treatments and can guide decisions on additional real-world studies that may be needed to show additional benefits. These studies can be especially beneficial in rare disease treatments where standard of care is often inadequate.
- **Disease and treatment/product registries** can be very useful in gathering data on patient usual care, current treatment landscapes, long-term clinical outcomes, etc., which can help rare disease manufacturers better understand the impact of the disease on patients and guide future RWE research needs. This is again very pertinent to rare diseases where information can be limited due to the scarcity of patients and challenges of collecting data from these patients. (See "Registries in Rare Disease Research – Approaches to Optimize Success" by Ross in this issue of *The Evidence Forum*.)

Early engagement in strategic real-world evidence generation planning, in the context of these new opportunities for market access optimization, will be paramount to ensure the right data are available to address peri- and post-approval questions related to product safety, effectiveness, and value. With Germany's increased focus on long-term, real-world data, manufacturers also need to sharpen their focus to be prepared for these new evidence demands. ■

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Upcoming Presentations

NCCN 2019 Annual Conference

March 21-23, 2019; Orlando, FL, USA

POSTER

Human Papillomavirus Status and Survival among Patients with Oropharyngeal Cancer: Analyses of a United States Health System

Aggarwal H, Li L, Cuyun Carter G, **Fraeman K, Berger A**

AMCP 2019 Annual Meeting

March 25-28, 2019; San Diego, CA, USA

POSTERS

Incidence and Cost of Major Cardiovascular Events among Patients with Chronic Coronary Artery Disease or Peripheral Artery Disease Identified in a Large United States Healthcare Database

Berger A, Bhagnani T, **Murphy B, Nordstrom B**, Zhao Q, Ting W, Leeper N, Berger J

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June 23-27, 2019;
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ICPE 2019

August 24-28, 2019;
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ISOQOL

October 20-23, 2019;
San Diego, CA, USA
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ISPOR 2019 Copenhagen

November 2-6, 2019;
Copenhagen, Denmark
www.ispor.org

Treatment Patterns and Unmet Need in Advanced Hepatocellular Carcinoma: Analysis of US Department of Defense Military Health System Data

Kim R, **Stokes M**, Marshall A, Wisniewski T, Gricar J, Savidge R, **Shah S, Mercaldi K, Schaumberg D**, Evans A, Mackie V

Budget Impact Analysis of One-Time Screening for Atrial Fibrillation

Oguz M, Lanitis T, Leipold R, Wygant G, Friend K, Li X, Hlavacek P, Mattke S, Singer DE

Factors that Impact Health-Related Quality of Life in Patients with Tardive Dyskinesia: Regression Analyses of Data from the Real-World RE-KINECT Study

Caroff S, Cutler A, Tanner C, **Shalhoub H, Lenderking WR, Yeomans K**, Anthony E, Yonan C

World Orphan Drug Congress USA

April 10-12, 2019; Oxon Hill, MD, USA

SPEAKERS

Patient-Focused Rare Disease Clinical Trial Protocols: Patient-Centered Outcomes and Beyond

Vernon M, Marsh K

2019 CADTH Symposium

April 14-16, 2019; Edmonton, Alberta, Canada

ISSUE PANEL

Should Suboptimal Clinical Evidence be Used to Inform HTA Recommendations?

Caro JJ, Desrosiers N, Chambers A, McCabe C

ACOG 2019

May 3-6, 2019; Nashville, TN, USA

POSTER

Elagolix Improves Quality of Life Among Uterine Fibroids Patients with Heavy Menstrual Bleeding in Phase 3 Trials

Al-Hendy A, Soliman AM, Wang H, **Coyne K**, Carr BR

National Kidney Foundation 2019 Spring Clinical Meetings

May 8-12, 2019; Boston, MA, USA

POSTERS

Targeted Literature Review of Patient-Reported Burden of Anemia in Chronic Kidney Disease

Anatchkova M, Arregui M, Brooks A, Michalopoulos S, Shafai G, Bozas A, Farag Y, Sanon M

Targeted Review of the Epidemiology and Burden of Anemia in Chronic Kidney Disease

Anatchkova M, Brooks A, Earley A, Michalopoulos S, Shafai G, Bozas A, Farag Y, Sanon M

ATS 2019

May 17-22, 2019; Dallas, TX, USA

POSTERS

Disease Status Affects Symptomatic Patients' Preferences for Maintenance Inhaler Therapies: Discrete Choice Experiment

Hanania NA, **Tervonen T**, Hawken N, Gilbert I, **Heidenreich S**, Martinez FJ

Quantifying Symptomatic Patients' Preferences for Maintenance Inhaler Therapies: Discrete Choice Experiment

Martinez FJ, **Tervonen T**, Hawken N, Gilbert I, **Heidenreich S**, Hanania NA

McGill University Pharmacoepidemiology Courses Summer Session

May 27-30, 2019; Montreal, Canada

SUMMER COURSE

EPIB 654 - Pharmacoeconomics for Health Technology Assessment

Caro JJ

HTAi 2019 Annual Meeting

June 15-19, 2019; Cologne, Germany

WORKSHOP

Discretely-Integrated Condition Event (DICE) Simulation for HTA

Caro JJ, Moller J

CIPP 18th International Congress on Pediatric Pulmonology

June 27-30, 2019; Tokyo, Japan

POSTER

Burden of Severe Asthma in Children in the English Primary Care Setting

Lenney W, Hattori T, Gokhale M, Evitt L, **Nordstrom B, Collins J, Schultze A**, Van Dyke MK

ISPOR 2019 Bogota

September 12-14, 2019; Bogotá, Colombia

SHORT COURSE

Applied Modeling

Instructor: **Caro JJ**

ARM Cell & Gene Meeting on the Mesa

October 2-4, 2019; Carlsbad, CA, USA

SPEAKER

Navigating Acceptance, Uptake and Affordability across the Lifecycle

Faulkner E, Doyle, J, Jacques L, Keith P, Philip R, Pinilla-Dominguez P, Powell R

Recent Presentations

World Pharma Pricing and Market Access

March 19-20, 2019; Amsterdam, Netherlands

SPEAKER

Early Integrated Scientific Advice: A Key to Optimal PRMA?

Bending M

DIA | MASC 2019

March 18-20, 2019; Orlando, FL, USA

POSTER

Conformance of AMCP Dossiers to Recommended Page Limits and Strategies Used to Streamline Presented Information

Hughes K, Murry T, Kovalycsik K, Murphy K, Saini S

ACC.19

March 16-18, 2019; New Orleans, LA, USA

POSTER

Incidence of Cardiovascular Events among Real-World Patients with Chronic Coronary Artery Disease or Peripheral Artery Disease Receiving Aspirin

Leeper N, Zhao Q, **Simpson A**, Ting W, **Murphy B**, Berger JS, **Berger A**

ISSWSH / ISSM 2019

March 7-10, 2019; Atlanta, GA, USA

POSTER

Conversations with Participants in the RECONNECT Studies about Their Experiences with Bremelanotide for Treatment of Hypoactive Sexual Desire Disorder

Koochaki P, **Revicki D**, Wilson H, **Pokrzywinski R**, Jordan R, Lucas J, Williams L, Krop J

ECCO 2019

March 6-9, 2019; Copenhagen, Denmark

POSTERS

Real-World Effectiveness and Safety of Vedolizumab and Anti-TNF in Biologic-Naive Crohn's Disease Patients: Results from the EVOLVE Study

Bressler B, Mantzaris G. Silverberg M, Zezos P, **Stein D, Colby C**, Lissoos T, Lopez C, Natsios A, Radulescu G, Patel H, Demuth D, Yarur A

Real-World Effectiveness and Safety of Vedolizumab and AntiTNF in Biologic-Naive Ulcerative Colitis Patients: Results from the EVOLVE Study

Yarur A, Mantzaris G, Silverberg M., Walshe M, Zezos P, **Stein D, Bassel M**, Lissoos T, Lopez C, Natsios A, Radulescu G, Patel H, Demuth D, Bressler B

Educational Workshop Organized by Saw Swee Hock School of Public Health & ISPOR Singapore Chapter

February 26-27, 2019; Singapore

WORKSHOP

Advanced Modelling Techniques in Health Technology Assessments and Real-World Evidence Generation

Caro JJ

WORLD Symposium 2019

February 4-8, 2019; Orlando, FL, USA

POSTER

Saccadic Eye Movements and Their Use as Clinical Endpoints in Lysosomal Storage Disorders: A Literature Review

Nalysnyk L, Hamed A, Rochmann C, **Molenkamp L, Rawson K**, Fischer T

DIA Pharmacovigilance and Risk Management Strategies Conference

January 28-30, 2019; Washington, DC, USA

SPEAKER

Validating a Self-Report Measure of Prescription Opioid Misuse and Abuse (the POMAQ) in Patients with Chronic Noncancer Pain: Pathways to Success

Coyne K

Phacilitate Leaders World 2019

January 22-25, 2019; Miami, FL, USA

SPEAKER

Aligning Regulatory, Value Demonstration and Market Access Strategy to Drive Uptake of Advanced Therapies: What Do Executives Need to Know?

Faulkner E, Daniel G, Hurley P

ASH Annual Meeting

December 1-4, 2018; San Diego, CA, USA

POSTERS

Health-Related Quality of Life among Patients with Relapsed or Refractory Multiple Myeloma Who Received Pomalidomide, Bortezomib, and Low-Dose Dexamethasone versus Bortezomib and Low-Dose Dexamethasone - Results from the Phase 3 OPTIMISMM Study

Weisel K, Dimopoulos M, Moreau P, Yagci M, Larocca A, Kanate AS, Vural F, Cascavilla N, Basu S, Johnson P, Byeff P, Hus M, Rodríguez-Otero P, Matsue K, Muelduer E, Anttila P, Hayden P, Krauth MT, Ben-Yehuda D, Mendeleeva L, **Guo S**, Purnomo L, Yu X, Grote L, Biyukov T, Zaki M, Richardson P

Treatment in AML and MDS Patients Who Are Ineligible for Intensive Chemotherapy: Using Social Media Intelligence to Capture What Really Matters to Patients

Booth A, Bell TJ, **Halhol S**, **Pan S,** Welch VL, **Merinopoulou E, Lambrelli D, Cox A**

Using Social Media to Highlight Unmet Needs in Patients with AML and MDS Ineligible for Intensive Chemotherapy: A Patient Centered Perspective

Booth A, Bell TJ, **Halhol S**, **Pan S,** Welch VL, **Merinopoulou E, Lambrelli D, Cox A**

ORAL PRESENTATION

The Impact of Lenalidomide, Bortezomib, and Dexamethasone Treatment on Health-Related Quality of Life in Transplant-Eligible Patients with Newly Diagnosed Multiple Myeloma: Results from the IFM/DFCI 2009 Trial

Roussel M, Hebraud B, Hulin C, Perrot A, Caillot D, Macro M, Arnulf B, Belhadj K, Garderet L, Facon T, **Guo S, Altincatal A**, Dhanasiri S, Leleu X, Moreau P, Attal M

4th European Conference on Monitoring the Effectiveness of Risk Minimization

November 19-21, 2018; London, UK

ORAL PRESENTATION

Use of Surveys to Evaluate the Effectiveness of Risk Minimization Measures: The Perspective of ISPE Special Interest Group, BRACE

Rubino A

28th Alzheimer Europe Conference

October 29-31, 2018; Barcelona, Spain

POSTER

Identifying Patients at Higher Risk of Initiating Cognitive Decline for Evaluating Amyloid-Targeted Treatments

Tafazzoli A, Kansal A, Weng J, Ishak J

ACPE 2018 - ISPE's Asian Conference on Pharmacoepidemiology

October 27-29, 2018; Xi'an, China

POSTER

Feasibility Assessment for an Observational Study Evaluating Effectiveness/Safety of a Fifth-Generation Cephalosporin Antibiotic in Community-Acquired Pneumonia (CAP) Patients in China

Gu Y, **Stein D, Soni M, Simeone JC**

ISOQOL 2018 25th Annual Conference

October 24-27, 2018; Dublin, Ireland

WORKSHOPS

Clinical Outcome Assessment in a Multi-Cultural Context: Measurement Challenges and Solutions

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

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

Hareendran A, Skalicky A, Magasi S

POSTERS

Development of a Patient Reported Measure of Quality of Care Transitions: Evidence of Structural Validity

Anatchkova M, Atkinson M, Santry H, Erskine N, Kiefe C

The American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index-Daily Diary (ANMS GCSI-DD): Assessing Qualitative Validity and Electronic Usability in Patients with Idiopathic or Diabetic Gastroparesis

Revicki DA, Speck RM, Lavoie S, Puelles J, Kuo B, Camilleri M, Parkman HP

CTAD 2018

October 24-27, 2018; Barcelona, Spain

POSTER

Validating Simulated Cognition Trajectories Based on ADNI Against Trajectories from the National Alzheimer's Coordinating Center (NACC) Dataset

Tafazzoli A, Weng J, Sutton K, Litkiewicz M, Chavan A, Krotneva M, Kansal A

ASN Kidney Week 2018

October 23-28, 2018; San Diego, CA, USA

POSTERS

Associations of Anemia with Quality of Life in CKD Stage 3-5 Patients: Results from CKDopps in the US and Brazil

Sukul N, Muenz D, Speyer E, Lopes A, Asahi K, Hoshino J, **Dhalwani N**, van Haalen H, Pecoits-Filho R, Bieber B, Robinson BM, Pisoni RL

The Impact of Newly Developed Inflammation, Characterized by Rise in C-Reactive Protein, on Anemia Management Practices in Hemodialysis Patients: A Before-After Design in the DOPPS

Karaboyas A, Morgenstern H, Vanholder RC, Fleischer NL, Schaubel DE, Schaeffner E, Akizawa T, **Dhalwani NN**, Sinsakul MV, Pisoni RL, Robinson BM

AMCP Nexus 2018

October 22-25, 2018; Orlando, FL, USA

POSTERS

A Cost-Consequence Analysis of Bictegravir/Emtricitabine/Tenofovir Alafenamide (BIC/FTC/TAF) Compared with Other Antiretroviral Regimens in a Simulated Model of Adult HIV Patients

Dejesus E, **Folse H**, Altice F

An Economic Evaluation of Tofacitinib for the Treatment of Moderate to Severely Active Ulcerative Colitis: Modeling the Cost of Treatment Strategies in the United States (*Bronze Medal Winner)

Milev S, DiBonaventura M, **Quon P, Goh JW**, Bourret J, Peeples-Lamirande K, Soonasra A, Cappelleri JC, Quirk D

Budget Impact Analysis of Moxetumomab Pasudotox-TDFK for the Treatment of Patients with Relapsed or Refractory Hairy Cell Leukemia in the United States

Tafazzoli A, Kempster J, Pavilack M, **Deger K**, Ma W, Olufade T

Recent Publications in Rare Diseases

Gelhorn HL, Ye X, **Speck RM**, Tong S, Healey JH, Bukata SV, Lackman RD, **Murray L**, Maclaine G, **Lenderking WR**, Hsu HH, Lin PS, Tap WD. The Measurement of Physical Functioning among Patients with Tenosynovial Giant Cell Tumor (TGCT) Using the Patient-Reported Outcomes Measurement Information System (PROMIS). *J Patient Rep Outcomes.* 2019 Feb 4;3(1):6. doi: 10.1186/s41687-019-0099-0.

Lund AM, Borgwardt L, Cattaneo F, Ardigò D, Geraci S, Gil-Campos M, De Meirleir L, Laroche C, Dolhem P, Cole D, Tylki-Szymanska A, Lopez-Rodriguez M, Guillén-Navarro E, Dali CI, Héron B, Fogh J, Muschol N, Phillips D, Van den Hout JMH, Jones SA, Amraoui Y. Comprehensive Long-Term Efficacy and Safety of Recombinant Human Alpha-Mannosidase (Velmanase Alfa) Treatment in Patients with Alpha-Mannosidosis. *J Inherit Metab Dis.* 2018 Nov;41(6):1225-1233. doi: 10.1007/s10545-018-0175-2.

Marshall RD, Collins A, Escolar ML, Jinnah HA, Klopstock T, Kruer MC, Videnovic A, Robichaux-Viehoever A, **Swett L, Revicki DA**, Bender RH, **Lenderking WR**. A Scale to Assess Activities of Daily Living in Pantothenate Kinase-Associated Neurodegeneration. *Mov Disord Clin Pract.* 2019 Jan 22;6(2):139-149. doi: 10.1002/mdc3.12716. eCollection 2019 Feb.

Mattera M, **Vernon MK, Raluy-Callado M**, Mikl J. Validation of the Shortened Hunter Syndrome-Functional Outcomes for Clinical Understanding Scale (HS-FOCUS). *Health Qual Life Outcomes.* 2018 Nov 8;16(1):209. doi: 10.1186/s12955-018-1006-8.

Nalysnyk L, Sugarman R, **Cele C**, Uyei J, **Ward A**. Budget Impact Analysis of Eliglustat for the Treatment of Gaucher Disease Type 1 in the United States. *J Manag Care Spec Pharm.* 2018 Oct;24(10):1002-1008. doi: 10.18553/jmcp.2018.24.10.1002.

Planté-Bordeneuve V, Lin H, Gollob J, Agarwal S, **Betts M, Fahrbach K, Chitnis M**, Polydefkis M. An Indirect Treatment Comparison of the Efficacy of Patisiran and Tafamidis for the Treatment of Hereditary Transthyretin-Mediated Amyloidosis with Polyneuropathy. *Expert Opin Pharmacother.* 2019 Mar;20(4):473-481. doi: 10.1080/14656566.2018.1554648. Epub 2018 Dec12.

Rentz AM, Skalicky AM, Liu Z, Dunn DW, Frost MD, Nakagawa JA, Prestifilippo J, Said Q, Wheless JW. Burden of Renal Angiomyolipomas Associated with Tuberous Sclerosis Complex: Results of a Patient and Caregiver Survey. *J Patient Rep Outcomes.* 2018 Jul 13; 2:30. doi: 10.1186/s41687-018-0055-4. eCollection 2018 Dec.

Rubin J, O'Callaghan L, **Pelligra C**, Konstan MW, **Ward A, Ishak JK, Chandler C**, Liou TG. Modeling Long-Term Health Outcomes of Patients with Cystic Fibrosis Homozygous for F508del-CFTR Treated with Lumacaftor/Ivacaftor. *Ther Adv Respir Dis.* 2019 Feb; doi: 10.1177/1753466618820186.

Skalicky AM, Rentz AM, Liu Z, Said Q, Nakagawa JA, Frost MD, Wheless JW, Dunn DW. Economic Burden, Work and School Productivity in Individuals with Tuberous Sclerosis and Their Families. *J Med Econ.* 2018 Oct;21(10):953-959. doi: 10.1080/13696998.2018.1487447.

Stewart M, **Shaffer S, Murphy B**, Loftus J, Alvir J, Cicchetti M, **Lenderking WR**. Characterizing the High Disease Burden of Transthyretin Amyloidosis for Patients and Caregivers. *Neurol Ther.* 2018 Dec;7(2):349-364. doi: 10.1007/s40120-018-0106-z.

Recent Publications

Abu HO, **Anatchkova MD**, Erskine NA, Lewis J, McManus DD, Kiefe CI, Santry HP. Are We "Missing the Big Picture" in Transitions of Care? Perspectives of Healthcare Providers Managing Patients with Unplanned Hospitalization. *Appl Nurs Res.* 2018 Dec; 44:60-66. doi: 10.1016/j.apnr.2018.09.006.

Anatchkova M, Brooks A, Swett L, Hartry A, Duffy RA, Baker RA, Hammer-Helmich L, Sanon Aigbogun M. Agitation in Patients with Dementia: A Systematic Review of Epidemiology and Association with Severity and Course. *International Psychogeriatrics.* [In Press]

Anatchkova M, Donelson SM, **Skalicky AM, McHorney CA**, Jagun D, Whiteley J. Exploring the Implementation of Patient-Reported Outcome Measures in Cancer Care: Need for More Real-World Evidence Results in the Peer Reviewed Literature. *J Patient Rep Outcomes.* 2018 Dec 27;2(1):64. doi: 10.1186/s41687-018-0091-0.

Antonini A, Stoessl AJ, **Kleinman LS, Skalicky AM**, Marshall TS, Sail KR, Onuk K, Odin PLA. Developing Consensus among Movement Disorder Specialists on Clinical Indicators for Identification and Management of Advanced Parkinson's Disease: A Multi-Country Delphi-Panel Approach. *Curr Med Res Opin.* 2018 Dec;34(12):2063-2073.

Ashaye AO, Khankhel Z, Xu Y, **Fahrbach K**, Mokgokong R, Orme ME, Lang K, Cappelleri JC, Mamolo C. A Comparative Evaluation of Gemtuzumab Ozogamicin + Daunorubicin-Cytarabine and Other Treatments for Newly Diagnosed Acute Myeloid Leukemia. *Future Oncol.* 2019 Feb;15(6):663-681. doi: 10.2217/fon-2018-0512.

Basile J, Egan B, Punzi H, Ali S, **Li Q**, Patel M, Neutel J. Risk of Hospitalization for Cardiovascular Events with β-Blockers in Hypertensive Patients: A Retrospective Cohort Study. *Cardiol Ther.* 2018 Dec;7(2):173-183. doi: 10.1007/s40119-018-0117-y.

Betts MB, Milev S, Hoog M, Jung H, **Milenković D**, Qian Y, Tai MH, Kutikova L, Villa G, Edwards C. Comparison of Recommendations and Use of Cardiovascular Risk Equations by Health Technology Assessment Agencies and Clinical Guidelines. *Value Health.* 2019 Feb;22(2):210-219. doi: 10.1016/j.jval.2018.08.003.

Bonine NG, **Berger A, Altincatal A**, Wang R, Bhagnani T, Gillard P, Lodise T. Impact of Delayed Appropriate Antibiotic Therapy on Patient Outcomes by Antibiotic Resistance Status from Serious Gram-negative Bacterial Infections. *Am J Med Sci.* 2019 Feb;357(2):103-110. doi: 10.1016/j.amjms.2018.11.009.

Caro JJ, Brazier JE, Karnon J, Kolominsky-Rabas P, McGuire AJ, Nord E, Schlander M. Determining Value in Health Technology Assessment: Stay the Course or Tack Away? *Pharmacoeconomics.* 2019 Mar;37(3):293-299. doi: 10.1007/s40273-018-0742-2.

Cella D, Wilson H, **Shalhoub H, Revicki DA**, Cappelleri JC, Bushmakin AG, Kudlacz E, Hsu MA. Content Validity and Psychometric Evaluation of Functional Assessment of Chronic Illness Therapy-Fatigue in Patients with Psoriatic Arthritis. *J Patient Rep Outcomes.* 2019 Jan 24;3(1):5. doi: 10.1186/s41687-019-0094-5.

Chin KM, Gomberg-Maitland M, Channick RN, Cuttica MJ, Fischer A, Frantz RP, Hunsche E, **Kleinman L**, McConnell JW, McLaughlin VV, Miller CE, Zamanian RT, Zastrow MS, Badesch DB. Psychometric Validation of the Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT®) Questionnaire: Results of the SYMPHONY Trial. *Chest.* 2018 Oct;154(4):848-861. doi: 10.1016/j.chest.2018.04.027.

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de Boer IH, Zelnick LR, Lin J, **Schaumberg D**, Wang L, Ruzinski J, Friedenberg G, Duszlak J, Bubes VY, Hoofnagle AN, Thadhani R, Glynn RJ, Buring JE, Sesso H, Manson JE. Vitamin D and OmegA-3 Trial to Prevent and Treat Diabetic Kidney Disease: Rationale, Design, and Baseline Characteristics. *Contemp Clin Trials.* 2018 Nov; 74:11-17. doi: 10.1016/j.cct.2018.09.014.

DeMeo DL, Ramagopalan S, Kavati A, Vegesna A, Han MK, Yadao A, **Wilcox TK**, Make BJ; COPDGene Investigators. Women Manifest More Severe COPD Symptoms Across the Life Course. *Int J Chron Obstruct Pulmon Dis.* 2018 Oct 1; 13:3021-3029. doi: 10.2147/COPD.S160270. eCollection 2018.

Galipeau N, Klooster B, Krohe M, Tang DH, **Revicki DA**, Cella D. Understanding Key Symptoms, Side Effects, and Impacts of HR+/HER2- Advanced Breast Cancer: Qualitative Study Findings. *J Patient Rep Outcomes.* 2019 Feb 7;3(1):10. doi: 10.1186/s41687-019-0098-1.

Ghabri S, Stevenson M, **Möller J, Caro JJ**. Trusting the Results of Model-Based Economic Analyses: Is There a Pragmatic Validation Solution? *Pharmacoeconomics.* 2019 Jan;37(1):1-6. doi: 10.1007/s40273-018-0711-9.

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Graham S, McDonald L, **Wasiak R**, Lees M, Ramagopalan S. Time to Really Share Real-World Data? *F1000Res.* 2018 Jul 11; 7:1054. doi: 10.12688/f1000research.15517.1. eCollection 2018.

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Hareendran A, Skalicky A, Mannix S, Lavoie S, Desai P, Bayliss M, Thach AV, Mikol DD, Buse DC. Development of a New Tool for Evaluating the Benefit of Preventive Treatments for Migraine on Functional Outcomes - The Migraine Functional Impact Questionnaire (MFIQ). *Headache.* 2018 Nov;58(10):1612-1628. doi: 10.1111/head.13420.

Ishak KJ, Rael M, Hicks M, Mittal S, Eatock M, Valle JW. Relative Effectiveness of Sunitinib versus Everolimus in Advanced Pancreatic Neuroendocrine Tumors: An Updated Matching-Adjusted Indirect Comparison. *J Comp Eff Res.* 2018 Oct;7(10):947-958. doi: 10.2217/cer-2018-0020.

Kaufman HL, Schwartz LH, William WN Jr, Sznol M, **Fahrbach K**, Xu Y, Masson E, Vergara-Silva A. Evaluation of Classical Clinical Endpoints as Surrogates for Overall Survival in Patients Treated with Immune Checkpoint Blockers: A Systematic Review and Meta-Analysis. *J Cancer Res Clin Oncol.* 2018 Nov;144(11):2245-2261. doi: 10.1007/s00432-018-2738-x.

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Li T, **Franco-Villalobos C, Proskorovsky I, Sorensen SV**, Tran N, Sulur G, Chi KN. Medical Resource Utilization of Abiraterone Acetate Plus Prednisone Added to Androgen Deprivation Therapy in Metastatic Castration-Naive Prostate Cancer: Results from LATITUDE. *Cancer.* 2019 Feb 15;125(4):626-632. doi: 10.1002/cncr.31847.

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Loftus J, Camacho-Hubner C, Hey-Hadavi J, **Goodrich K**. Targeted Literature Review of the Humanistic and Economic Burden of Adult Growth Hormone Deficiency. *Curr Med Res Opin*. 2018 Nov 9:1-29. doi: 10.1080/03007995.2018.1546682. [Epub ahead of print]

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Collaboration with China-Based HLT Creates Opportunity to Expand Access to Real-World Data and Patients in China

PPD and Happy Life Tech (HLT), a Chinese medical AI company dedicated to transforming the relationship between humans and diseases, have entered into an exclusive and unique collaboration to create data science-driven clinical and real-world evidence solutions. This agreement pairs HLT's data technology and artificial intelligence with PPD's global expertise in clinical trials and real-world evidence generation.

HLT has a particularly strong depth of data and experience in oncology, immunology, and rare diseases, in addition to several other therapeutic areas that are currently being enhanced. They have relationships with more than 100 leading hospitals across over 20 provinces in China, which have the potential to yield quick capture of new drug uptake.

As PPD's Peri- and Post-Approval business unit, Evidera is excited about the potential this collaboration can offer our clients. Expanded access to China's evolving drug development and post-marketing ecosystem deepens our ability to help our clients generate the evidence needed to optimize the market access and commercial potential of their products on a global scale.

The press release announcing this collaboration can be read at:
https://www.ppdi.com/news-and-events/news/2019/ppd-and-hlt-agreement

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For more information, please contact us at info@evidera.com.

About HLT

HLT is a leading medical AI company dedicated to transforming the relationship between humans and diseases. HLT has in-depth cooperation with regulators, universities and research institutes in China and other countries. Full lifecycle solutions of HLT, including clinical trials, post-launch development of drugs, product launch and real-world studies, significantly accelerate the process of new drug development. In addition, HLT's reports based on real-world insights have been published in *The Lancet Oncology, Nature Medicine* and other top journals. For more information, visit http://www.happylifetech.com/.

Evidera Welcomes New Senior Staff

Syed Aziz, MSc
Head of Peri- and Post-Approval Studies
Technology Solutions
Real-World Evidence

Mr. Aziz is Head of Technology Solutions for Evidera's Peri- and Post-Approval Studies (PPAS), based in London, and is responsible for devising the technology strategy and providing technology leadership in this area. He is involved in multiple technology initiatives including developing capabilities for improving access to real-world data, identifying opportunities to use machine learning and artificial intelligence (AI) to improve client offerings, and improving patient engagement and reporting during study execution. Mr. Aziz is a technology leader with extensive experience in delivering enterprise-wide technology solutions. In his recent roles, he has been involved in establishing a technology function for a leading clinical research organization, which involved setting up software engineering teams, driving technology strategy, and helping establish a culture of innovation through adoption of proven industry practices such as Agile software development, behavior driven development, and DevOps. Mr. Aziz has led a diverse team of technologists with a broad range of skills from UX design to web development and data engineering and is able to work closely with the technology teams given his own software development background. He has several years of experience delivering technology solutions for various industry verticals including healthcare, oil and gas, gravel, retail, and telecommunications. He is a software engineering graduate from University of Oxford and has hands-on experience with Java, Scala, PHP and Python. Over the years, he has mentored teams focusing on domains such as software development methodologies, system architecture and design, application development, data integration, and information security.

Matthew Bending, PhD
Senior Principal and
Executive Director of HTA Strategy
Market Access Consulting

Dr. Bending is a Senior Principal and the Executive Director of HTA Strategy in Evidera's London office, bringing over 14 years of consulting experience to the team. As a health economist with a doctorate in health sciences where he studied the use of health technology assessment (HTA) in reimbursement decision-making, he is well positioned to provide senior leadership for large projects on HTA strategy and integrated scientific advice in a variety of therapeutic areas. His experience is wide-ranging, including projects for HTA scientific advice alone, for multiple HTAs, and in parallel and jointly with regulatory scientific advice. Additionally, he has led projects in value proposition development, HTA policy, HTA landscaping, HTA evidence generation gap analysis, evidence synthesis, health economic modeling, and payer advisory boards. He has held more than 10 integrated scientific advice roundtable events, presented at international conferences, and published over 35 reports/papers on HTA and HEOR topics. Dr. Bending was a co-author of a study that won the Egon Jonsson award in 2009/2010 for the most outstanding manuscript published in the *International Journal of Technology Assessment in Health Care* on the harmonisation of HTA internationally. Prior to joining Evidera, Dr. Bending developed the early integrated HTA scientific practice at ICON plc. and led the Mapi Group HTA, Strategy and Communication team. He was a senior consultant at the York Health Economics Consortium at the University of York leading projects for the National Institute for Health and Care Excellence, Department of Health, Patient Safety and Research Portfolio and General Medical Council. Dr. Bending has a PhD in health sciences from the University of York, and an MSc in economics and BSc honours in economics from the University of Warwick.

Seema Buckley, GPhC, MSc

Principal
Market Access Consulting

Ms. Buckley is a Principal with the Market Access Consulting team in Evidera's London office where she is responsible for directing market access projects, identifying strategic recommendations, and providing guidance as a UK Health Adviser. Ms. Buckley is an accomplished healthcare executive with 20 years' experience in healthcare management, working in both NHS and private sectors; in primary, secondary, tertiary care services; and as a payer. She is experienced in the design, delivery, and review of health care programs, health strategy and healthcare services. Ms. Buckley has expertise in market access, pathway development, and decision making in the NHS, with experience across a wide range of disease areas. Most recently, Ms. Buckley was Chief Pharmacist and Director of Commissioning for Kingston, with the statutory responsibility for the medicines budget and development of care pathways for the area. Through her collaborative leadership style and strong clinician engagement, she has led many successful pathway reviews leading to improvements with measurable impact on population health and improved resource utilization. Prior to her roles in strategic payer organizations, Ms. Buckley worked as a clinical pharmacist in many of London's teaching hospitals including Guy's and St Thomas', St Bartholomew's, and King's College Hospital. She was previously a Medicines Prescribing Associate with the National Institute for Health and Clinical Excellence and a National Pharmaceutical Adviser to NHS England. Ms. Buckley holds an MSc in clinical pharmacy and a Bachelors of Pharmacy (Honours) from University College London. Her areas of personal interest include health care planning and continuous quality improvement.

Lael Cragin, MPH

Research Scientist
Evidence Synthesis, Modeling & Communication

Ms. Cragin is a Research Scientist in Evidera's Bethesda, Maryland, office. Her responsibilities include leading the development of health economic models of new and established products for submission to reimbursement agencies and other decision-makers worldwide, as well as the dissemination of model results in the form of technical reports and manuscripts. In addition, she has extensive experience in the conduct of systematic literature reviews and the preparation of AMCP and global value dossiers. Her work for biopharmaceutical, medical device, and diagnostic companies has spanned numerous therapeutic areas, including chronic and acute infectious diseases. Ms. Cragin has published in journals such as *BMC Infectious Diseases, HIV Clinical Trials,* and *American Journal of Health-System Pharmacy* and has presented at various economic and clinical conferences. She received an MPH in epidemiology from Emory University's Rollins School of Public Health, a BA magna cum laude in economics from Boston College, and studied for a year at Oxford University. Prior to her current role, Ms. Cragin worked as an epidemiologist/ statistician at Grady Hospital System in Atlanta, Georgia, and as an analyst in the economic analysis group at Arthur Andersen LLP.

Ananth Kadambi, PhD

Senior Research Scientist

Evidence Synthesis, Modeling & Communication

Dr. Kadambi is a Senior Research Scientist in Evidera's San Francisco office and has more than 15 years of experience in modeling and simulation and its applications, including decision tree, state-transition (i.e., Markov), and discrete event simulation (DES) approaches to health economic modeling. Specifically, he has led the development of cost-effectiveness models for drugs for oncology and cardiovascular indications that were used to support HTA submissions to the National Institute of Clinical Excellence (NICE) and the Canadian Agency for Drugs and Technologies in Health (CADTH), respectively. Dr. Kadambi previously worked for Evidera as a director of modeling and simulation development and a research scientist, where he led cross-functional teams responsible for the development of global cost-effectiveness and budget-impact models in multiple therapeutic areas, economic analyses alongside clinical trials, systematic literature reviews, and complex statistical analyses. He also led the development of initiatives within Evidera on novel simulation techniques, including clinical trial simulation. He has held former roles in industry, including senior vice president, PhysioPD™ at Rosa & Co., LLC and vice president of R&D at Entelos Inc. In both roles, he held wide-ranging executive management and project leadership responsibilities. Dr. Kadambi's scientific expertise includes inflammation, cardiovascular disease, and cancer biology, and he has co-authored many published peer-reviewed manuscripts in life science, modeling, and health economic journals. Dr. Kadambi completed his PhD in biomedical engineering at the University of Virginia, Charlottesville, Virginia, where he focused on the study of inflammation and mammalian vasculature. He then completed two postdoctoral fellowships at Massachusetts General Hospital and the University of California, San Francisco, focusing on oncology.

Martin Ladouceur, PhD

Research Scientist

Real-World Evidence

Dr. Ladouceur is a Research Scientist in our Montreal, Canada, office and is a methodologist specialized in health research, with over 10 years of applied experience in clinical research and consulting. He currently leads and collaborates on several retrospective chart review projects in Crohn's disease, collaborates on oncology projects, and supervises younger scientific staff. Before joining Evidera, Dr. Ladouceur was a consultant in health economic and outcome research at Analysis Group Inc., where he led real-world evidence studies (burden of disease, treatment patterns, efficacy and safety, unmet needs, etc.) in a variety of therapeutic areas and managed studies such as prospective studies, matching-adjusted indirect comparisons, chart reviews, retrospective studies using administrative databases, clinical trials, and targeted literature reviews. Dr. Ladouceur has served as the principal consultant at an academic research hospital (CR-CHUM) where he collaborated with clinicians and researchers on all phases of clinical research projects, and he has played a major role in the design of a crossover trial on artificial pancreatic and nutrition/exercise projects involving patients with type 2 diabetes. His collaborative work led to several grants from organizations such as the National Institute of Health, the Canadian Institute of Health Research, Cystic Fibrosis Foundation, Canadian Diabetes Association, and Genome Canada, for a total of over 12 million dollars, and his research has been published in several top journals. Dr. Ladouceur trained in biostatistics at McGill University and pursued postdoctoral training in statistical genetics at the Montreal Jewish Hospital, University of Toronto, and INSERM, Paris. He has taught several graduate biostatistics classes at McGill and Montreal University and is an adjunct clinical professor at Montreal University at the School of Public Health.

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