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Early Access Programs
Opportunities and Challenges for Real-World Data Collection

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What are Early Access Programs?

For patients with serious or life-threatening diseases who have exhausted all treatment options and who are not eligible for trial participation, early access programs can provide them with investigational treatments (pre-launch and/or prior to country approval).[1-3] Definitions and nomenclature of early access programs vary by country and many pathways exist for patients to gain early access to medicines. Each pathway is governed by different regulatory bodies; therefore, several guidelines exist around the approval, set-up, conduct, and structure of these programs. Early access programs may be implemented at different stages of the product life cycle, including prior to, during, and after the regulatory submission process for market authorization *(Figure 1)*.

Since many countries have lengthy periods between initial marketing authorization and country approvals and reimbursement,[1,4] the number of early access programs being initiated by pharmaceutical companies are increasing to bridge the treatment availability gap between clinical trials and market-uptake. Through early access programs, patients who have either already benefitted from clinical trial agents or patients who demonstrate unmet need can receive promising new treatments.

In addition to providing early access to treatment, these programs also offer a unique opportunity to evaluate clinical and safety outcomes outside of the clinical trial setting, without the constraints of strict inclusion and exclusion criteria. Data collected in these studies are viewed by some as proxies for real-world use because there is an opportunity to observe the potential benefits of an investigational treatment in a wider range of populations or for other indications.

Data Collection within Early Access Programs

Guidelines for Data Collection Provided by Program Regulators

Data collection guidelines within early access programs tend to vary by country, and within the European Union (EU), they also vary by member state *(Table 1)*. Across most types of early access programs, safety data collection is required, however, guidance on acceptable effectiveness data collection is limited.[5] While the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) do not prohibit data collection beyond safety outcomes within their guidelines, they do state that data collected within these programs should not be a substitute for data collected in the trial setting.[6-8]


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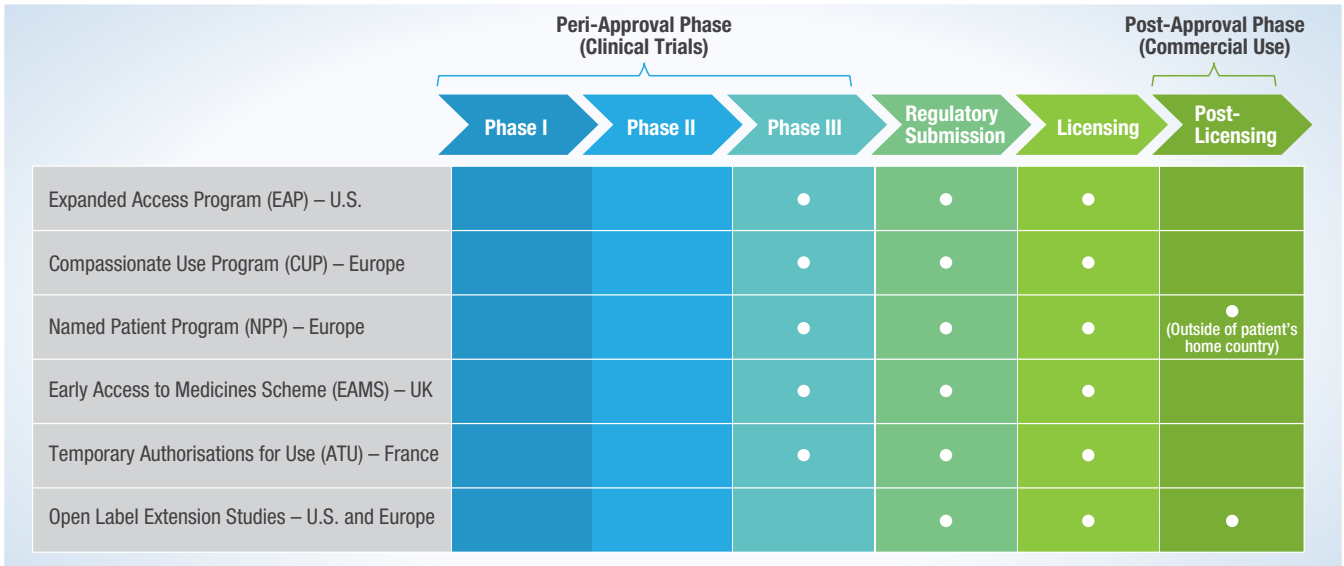
Figure 1. Early Access Programs Throughout the Product Life Cycle (U.S. and Europe)



More recently, the Early Access to Medicines Scheme (EAMS) in the United Kingdom (UK), governed by the Medicines and Healthcare Products Regulatory Agency (MHRA), established in 2014, asserted the importance of collecting additional supporting real-world data to provide additional knowledge of product value outside of a clinical trial setting.[9] The UK-based EAMS program is currently the only one of its kind to have issued guidelines for systematic collection of real-world data. The MHRA guidance highlights that data generated in EAMS can be used to facilitate National Institute for Clinical Excellence (NICE) Technology Appraisal. Additionally, these guidelines suggest that EAMS data collection must include, at a minimum, information on patient demographics, disease characteristics, dose and duration of treatment, comorbidities, concomitant medications, adverse events, and other factors known to be strongly predictive of efficacy or other outcomes of importance. Requirements for additional data collection (e.g., quality of life) in EAMS must be agreed upon by all parties including clinicians and patients, on a case-by-case basis.[10]

Published Data from Early Access Programs

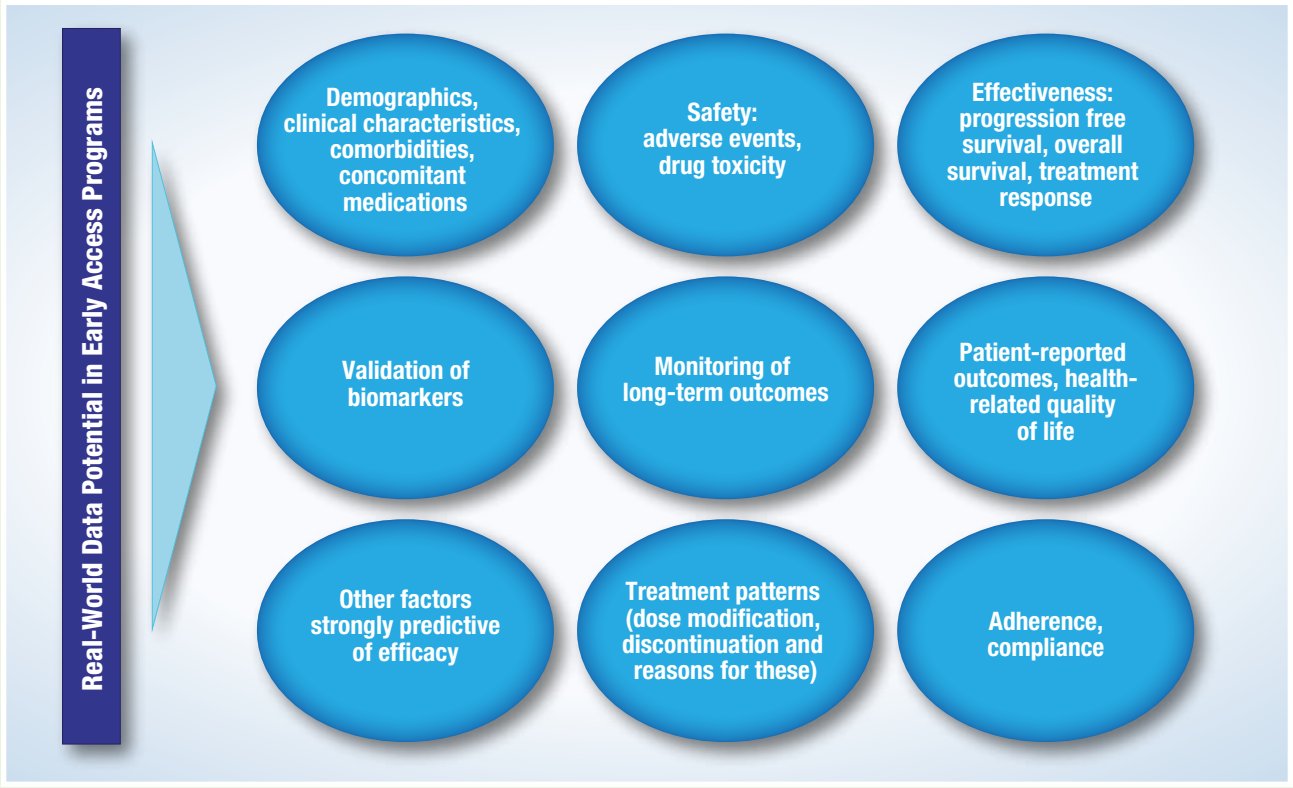
There is a breadth of published literature which summarizes the types of early access programs available and general overviews of these programs, including ethical considerations and operational challenges with set-up and conduct. To our knowledge, however, there is limited

Table 1. Data Collection Guidelines for Early Access Programs

	Expanded Access Program (EAP)	Compassionate Use Program (CUP) & Named Patient Program (NPP)	Temporary Authorisations for Use (ATU)	Early Access to Medicine Scheme (EAMS)
REGULATORY BODY	**FDA**	**EMA/CHMP/EU Member States**	**ANSM**	**MHRA**
DATA COLLECTION ↓				
Safety	✓ Required	✓ Depends on local requirement by member EU state	✓ Required	✓ Required and will be considered in regulatory submission
Effectiveness	✓ Allowed but not considered reliable evidence in regulatory submission	✓ Allowed but not considered reliable evidence in regulatory submission	• Patient characteristics and efficacy of medicinal product	✓ Allowed and will be considered in regulatory submission
Patient-Reported Outcomes (PROs)	• No clear guidelines	• No clear guidelines identified	• No clear guidelines identified	✓ Allowed subject to ethical approval. PROs will be considered in regulatory submission

ANSM=Agence Nationale de Sécurité du Medicament et des Poduits de Santé; **CHMP**=Committee for Medicinal Products for Human Use; **EMA**=European Medicines Agency; **EU**=European Union; **FDA**=Food and Drug Administration; **MHRA**=Medicines and Healthcare Products Regulatory Agency; **NHSE**=National Health Service England; **NICE**=National Institute for Health and Care Excellence

Figure 2. Potential Outcomes in Early Access Programs[29]



literature available which reports the findings of data collection within these programs. This is substantiated by a recent study (2017) which reported that only 2% (8/398) of early access programs registered in ClinicalTrials.gov reported up-to-date results for real-world data (RWD)-related outcomes,[11] illustrating the need for more transparency in data collection. Reluctance to report data collected in early access programs may be due to concerns with reliability and validity of this data, as well as lack of information pertaining to the relevance and application of these data to marketing authorizations. Since patients in early access programs are likely to be sicker (due to lack of therapeutic options available), they may be at higher risk for adverse events and/or to having lack of clinical response, which may make sponsors hesitant to collect and report on outcomes in these patient populations.[12]

> Although early access programs are not a substitute for data collection in clinical trials, they may be supplementary in addressing a variety of research questions…

In available publications of data collected in early access programs, some studies incorporated data collection from inception of the program,[13-19] while others implemented data collection via retrospective chart review once the program was complete.[20-26] In the majority of these studies, data were used as supplements to clinical trial findings in a real-world setting. For example, retrospective chart review studies in oncology CUP and NPP patient populations demonstrated similar effectiveness and safety profiles relative to the trial patients.[21-24] A recent chart review study in the U.S. also found that lung cancer patients enrolled into a clinical access program after having benefited from an investigational drug within a prior trial were able to see clinical benefit from investigational drug use through the program for more than 10 years.[25-26]

A review study conducted in 2017 compared the efficacy endpoints for anti-cancer drugs observed in CUPs versus clinical trials (U.S. and Europe); efficacy endpoints included overall survival, progression-free survival, and overall response, and over half of CUPs (5/9) reported better or equal efficacy compared to that reported in clinical trials.[27]

Research Questions in Early Access Programs

Although early access programs are not a substitute for data collection in clinical trials, they may be supplementary in addressing a variety of research questions, which could be informative for multiple stakeholders, including regulatory bodies, payers, clinicians, and patients. RWD collection in early access programs *(Figure 2)* has the potential to provide preliminary insight into:

- Whether the safety profile of the drug administered via early access program is similar to that observed in a trial setting and whether any new safety signals occur.[28]

- Treatment effectiveness (e.g., treatment response, overall survival) outside of the trial setting, including in sub-populations not included in clinical trials (children, older adults, those with comorbidities).
- Knowledge of the impact of the drug on quality of life in the pre-approval or peri-approval phase. This is relevant given the increasing importance placed on these outcomes in the post-approval phase.

To increase the reliability and validity of observational data collected in early access programs, the primary research questions and feasibility of data collection should be explored prior to implementation of the program. Furthermore, limitations of this data (e.g., uncontrolled exposures, potentially sicker patient population), should also be considered in regulatory submissions for market approval.

Considerations and Recommendations for Set-Up of Observational Research in Early Access Programs

Ethical Approval (for the Observational Study Component of the Early Access Program)

Since early access programs are not considered traditional research studies, they follow different rules and regulations for obtaining ethical approval. Ethical approval processes will also vary by country *(Figure 2)*.[6-9] If additional data collection is needed within an early access program, a protocol outlining plans for data collection will most likely need to be submitted to an ethics committee following the same pathway that would be used for an observational study. This protocol should be submitted in parallel with seeking approval for the launch of the early access program. Due to the unique nature of data collection in early access programs, it is essential to identify a key stakeholder contact to discuss the data collection plans and seek feedback on the ethics review and approval process to identify any uncertainties or hurdles that may arise.

If the ethics committee reviewing the observational study application is not able to fully understand the nature of the early access program and the plans for data collection, this may negatively impact the outcome of the ethics submission. Furthermore, ethics approval is time sensitive based on when the early access program will open. If stakeholders are not approached in a timely manner, then there is a risk that ethics approval may not be put in place in time for the opening of the program, limiting the potential for data collection.

Patient Consent

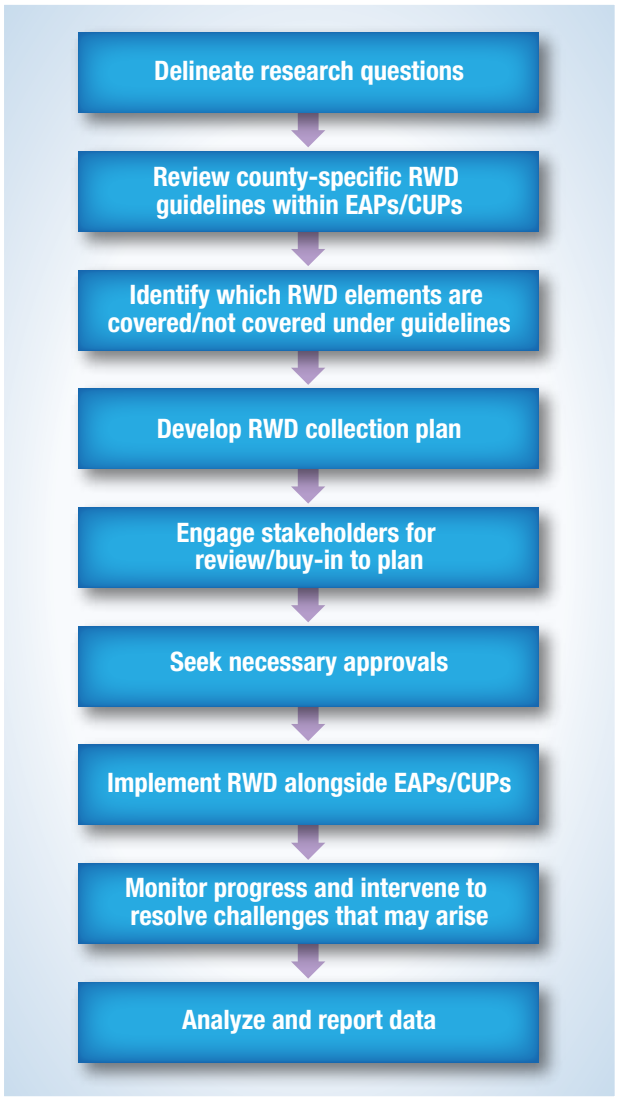
Different options for how to obtain patient consent for the additional data collection should be explored based on what is most feasible for the study. The consent form should clearly define all aspects of the data collection, including privacy, data elements to be collected, data

Spotlight Case Study

Incorporating Data Collection into Early Access Programs

To better understand the benefits of drug X in the pre-approval phase, Evidera recently collaborated with a pharmaceutical company to design and implement an early access program that integrated real-world clinical effectiveness and quality of life outcomes. During development of the data collection framework within this program, it was observed that published guidelines on the incorporation of data collection were lacking. Therefore, the process of framework development included the exploration and validation of the approach with key stakeholders (regulatory authorities, ethics, hospital systems). Figure 3 represents an overview of the steps taken, which led to successful approval and implementation of data collection within this early access program.

Figure 3. Recommended Steps to Successfully Incorporate RWD in Early Access Programs



source(s), timing of collection, and purpose of data collection (e.g., publication, HTA submission). It should be emphasized that the patient's ability to take part in the early access program overall is not contingent on whether or not they choose to take part in the observational research component of the program.

Data Collection Elements

It is important to determine which additional variables will be added to the study, what the data source will be, who will collect it, how it will be collected, and the timing for collection. Careful consideration for how the data will be used and challenges this may impose (that could negatively impact the program) is essential. Once the data elements are delineated, stakeholder feedback and approval from the regulatory authority that governs the early access program is needed. Secondary feedback and endorsement from clinician and hospital governing bodies is also recommended.

Site Set-Up and Training

Most often in early access programs, the request for drugs are patient/physician led, meaning that it is not possible to know in advance the hospitals or patients who will participate in these programs. This contrasts with observational studies wherein sites, patient population, and sample size are known prior to study initiation. This can add a complexity to setting up the RWD collection component of the study and may require special circumstance procedures for set-up of the study at the hospital and training of clinical staff.

In our experience, combining observational training with the early access program training was well received and efficient. In cases where set-up of the observational study at a site cannot happen in parallel to initiation of the early access program, sites should be reassured that they can proceed as planned with the early access program and without the additional data collection. This is important for ensuring that data collection does not hinder the patient receiving early access to the investigational drug.

Site and Patient Involvement

The level of effort and workload needed to collect the data must be carefully considered. Data collection from patient medical records should be kept to a few key outcomes measures (e.g., disease progression, survival status). Having physicians enter observational data through the same data collection tool as that required for other aspects of the early access program may be able to reduce data entry burden at sites.

Summary

Data collection within early access programs allows for generation of RWD prior to and after marketing authorization in patient populations with unmet need. RWD generated in the pre-approval phase could be used to supplement primary clinical trial outcomes in submissions for market approval and is useful for informing future real-world use. Additional guidance by regulatory bodies on how to enable and ensure consistency in data collection in early access programs is needed to improve validity of this research for regulatory submission. Data collection approaches must be scientifically robust, practical, and ethical. As the number of early access programs and the use of RWD to inform market access continues to grow, so will the benefits of collecting RWD in these programs. ■

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Are Patients at the Center of Your Trials?
Using Patient Engagement and Insights to Improve Clinical Research

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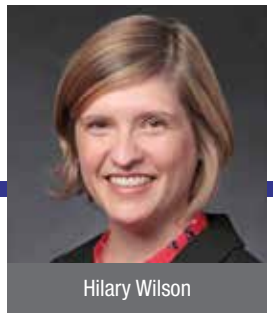
Patient-focused (also referred to as patient-centered): "ensuring that patients' experiences, perspectives, needs, and priorities are meaningfully incorporated into decisions and activities related to their health and well-being."[1]

As the cost associated with developing and launching medical products rises, and the treatment landscape becomes increasingly competitive, companies are looking for innovative and effective ways to accelerate drug development. Leveraging patient involvement early and often in medical product design is one approach to facilitate the development of a program that will increase enrollment, decrease drop-out, and demonstrate value of the product in the context of patient unmet needs. Patients in today's health care market are more knowledgeable about treatment options and have an increased voice in decision-making, and product success is contingent on designing ***patient-focused*** medicines that demonstrate value in terms of what is important to patients.

Patient-Focused Drug Development: How Did We Get Here, and Where are We Now?

The journey to patient-focused drug development dates back to the AIDS crisis, when the lack of treatment options, limited public research funding, and the time intensive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regulatory review process drove patient activists to organize and demand improvements to facilitate access to treatments. The movement was highly successful in driving change from a funding, regulatory, and public health perspective.[2] Since 1990, billions of federal dollars have been allocated to HIV research, prevention, and treatment programs through the Ryan White CARE Act.[3] Following significant lobbying and public demonstration efforts, the Parallel Track policy,[4] which expands availability of investigational drugs to people with AIDS/HIV that were not eligible to participate in clinical trials but did not have satisfactory alternative therapies, was approved in 1992. Shortly after, the Accelerated Approval policy[5] was implemented which allows approval of drugs based on surrogate endpoints that reasonably predict a drug provides clinical benefit. As a result of these and many other efforts of the collective movement, today there are over 30 products approved for the treatment of HIV/AIDS. In less than 30 years from the initial discovery of the virus, HIV/AIDS went from being a death sentence to a chronic disease where access to current treatments is available.

The efforts of the patient activists leading this movement laid the groundwork for patients and patient groups to engage in all aspects of medical product development – from early research and discovery, through market access and beyond. Today, efforts to facilitate ***patient engagement*** in medical product development are evident in a range of innovative programs across the spectrum.

There is increased funding for patient-centric research through organizations such as the Patient-Centered Outcomes Research Institute (PCORI)[6]; a myriad of efforts are available to educate patients on research, policy, and the life cycle of product development (e.g., European Patients' Academy on Therapeutic Innovation[7]); and a number of public/private partnerships have been established to further the patient engagement mission (e.g., Clinical Trials Transformation Initiative,[8] Patient-Focused Medicines Initiative[9]). Patient advocacy groups and disease foundations are increasingly directly leading medical product development activities and engaging with regulatory bodies and payer groups in these efforts.

Direct patient involvement in regulatory review and decision-making has also increased in recent years. Between 2011 and 2016, there was an 82% increase in the number of patient stakeholders that were involved in various European Medicines Agency (EMA) activities, and in 2016 alone, there were at least two patients or caregivers represented at six different product review meetings.[10] In the U.S., under the 2012 FDASIA reauthorization of the Prescription Drug User Fee Act (PDUFA),[11] the FDA pioneered the use of patient-focused drug development (PFDD) meetings to gather systematic input from patients and caregivers around unmet needs, experiences with existing treatments, and core impacts of the disease. Twenty-two meetings were hosted by the FDA between 2013 and 2017, the results of which may be leveraged in shaping a medical product program designed around patient needs. The 21st Century Cures Act of 2016 secured the opportunity for the FDA to expand the Patient-Focused Drug Development program, and has served as the impetus for many additional efforts to leverage the patient voice in the medical product review process. As of June 2017, all new drug approvals must include a brief statement summarizing any ***patient experience*** data that was submitted and reviewed as part of the application.[12]

Patient engagement (as defined in relation to the FDA's patient-focused drug development initiative): "activities that involve patient stakeholders sharing their experiences, perspectives, needs, and priorities that help inform FDA's public health mission. Such activities may include (but are not limited to): testimony at Advisory Committee meetings, submission to regulations.gov public docket; meetings attended by patients, FDA, and other stakeholders; other correspondence with FDA; interactions through social media; and interactions with or information from patient representatives or patient advocates."[1]

Patient Experience Data: *data that are collected by any persons and are intended to provide information about patients' experiences with a disease or condition. Patient experience data can be interpreted as information that captures patients' experiences, perspectives, needs, and priorities related to (but not limited to):*

1) the symptoms of their condition and its natural history;
2) the impact of the conditions on their functioning and quality of life;
3) their experience with treatments;
4) input on which outcomes are important to them;
5) patient preferences for outcomes and treatments; and,
6) the relative importance of any issue as defined by patients.[12]

With an expansion of the Patient Representative Program initiated under the FDA Safety and Innovation Act under Section 1137,[13] the FDA has the opportunity to have the patient at the table in deliberations with industry, ensuring that the patient voice is part of its interactions, discussions, and dialogue on new medical products. The FDA and EMA have also formed a patient engagement cluster to facilitate the sharing of best practices involving patients in the regulatory review process and advancing the patient engagement effort globally.[14]

Patient Engagement and Insights across the Product Life Cycle

The key to designing a patient-focused product is to engage with patients early and often, using both qualitative and quantitative approaches for gathering patient insights. To the degree possible, patient input should be considered in the design and execution of all patient experience activities outlined in *Figure 1*.

This paper focuses specifically on strategies to build a patient-centric clinical trial design, including Phase II-III trials, real-world evidence, and post-market approval studies.

Patient-Centric Trial Design

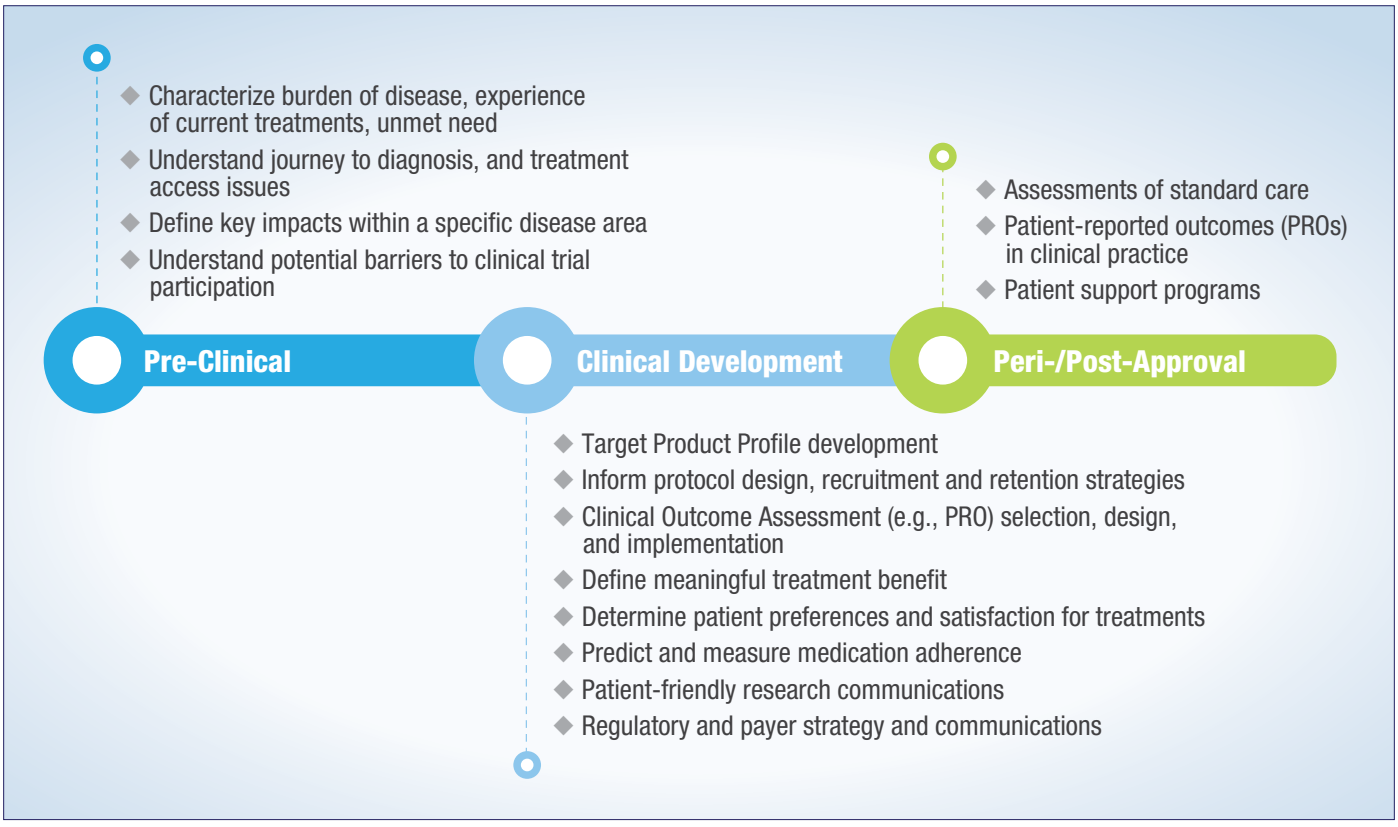
Patient-centric trials consider patient needs, perspectives, and priorities together with the scientific objectives of the study, from design through dissemination. They are designed to maximize the convenience of participating; accurately project enrollment; keep patients engaged from screening through completion; and, answer questions that are important from the patients' perspective. Key components and potential approaches to facilitating patient-centric trial design are discussed below.

Building Patient Communities

Patient-centricity begins with education and awareness. According to the National Institute of Health, only 15% of patients are aware that research is an option to them, with this percentage dropping in many therapeutic areas.[15] Additionally, research from Tufts suggests that only 0.2% of patients are referred to clinical trials, citing time and lack of information as a reason for their lack of referral.[16] These metrics paint a glaring picture of the industry-wide need to educate patients on clinical research as a treatment option and make the clinical trial process more patient-centric. This lack of awareness of clinical trials presents not only a chance to meet global unmet medical needs, but offers drug developers the opportunity to engage with research-naïve patient populations. This patient engagement begins with building patient communities by investing in global medical and social connection events. Establishing these communities and engaging with patients allows not only increased awareness, but the ability to harness the voice of the patient to understand how their needs can be better served.

The creation of patient communities happens when there is a commitment within research centers to engage with patients and by building established relationships with the medical community. With such a small percentage of patients being made aware of and participating in research, there is an obligation to ease the burden, improve the education, and increase the pathways for health care professionals to refer patients into studies. Social communities also need to be engaged to better understand other challenges of patient involvement, such as personal belief systems or economic drivers. Until communities are engaged, health checks are provided,

Figure 1. Patient Engagement and Insights across the Product Life Cycle



and advocacy groups are included as partners, the flow of patients into research centers will not be as successful. Ultimately, building patient communities takes time and perseverance, but if successful, a one-stop place for patients to access more research will be established.

Each patient community is different, and it is important to focus on the unique characteristics of that community. Through engagement, it is possible to discover what the local challenges might be, such as a prevalence of disease, a lack of transportation, economic challenges that affect time off for research needs, etc. With this knowledge, a place can be created for patients to come together and share experiences and resources. There is no more powerful voice in the research space than the patient who has been, or is currently, in a clinical trial. Through sharing their experiences with other potential trial participants, they can help other patients understand the research process and remove the myths and fear of the unknown. By creating these local community research centers and replicating that process across geographical locations, a system is constructed to increase patient awareness, ultimately leading to access to clinical trials and participation in the drug development process.

Protocol Design

To truly have a patient-centric approach to drug development, patients must have a seat at the table in protocol planning. Significant aspects of protocol design include determining whether the science is obtainable and the population exists in meaningful numbers. Including the patients' voice can help plan a protocol that has the widest acceptability among the target populations. There are a number of questions to be asked during the protocol design phase to ensure the focus on patient centricity is evident. Within the constraints of regulatory requirements, can the inclusion/exclusion criteria be tailored to increase the ease of enrollment? Can the logistics and visits be tailored to provide the best, most convenient patient experience? Both qualitative and quantitative research can help answer these questions. Access to a large sample set can provide statistically relevant input to guide the planning of a research program.

A key component in patient-centric studies is understanding the audience, including patients, clinicians, hospitals, etc. This is where a large, robust database of patients can be invaluable in understanding disease state and comorbidities. The addition of data from patients' online activities, purchasing patterns, interests, etc., can provide further understanding of the patient population and their experience. This additional information can ensure a rich assortment of patient types and insight into how to best tap into that population. When talking about big data, it is important to assess not only size but also appropriateness of the data to help find the patients needed.

Once Patients are Found, How Do You Keep Them?

Patient recruitment and enrollment is a huge goal, but only half the battle. Retaining patients in a trial is extremely important, and keeping them engaged throughout the process and ensuring they complete the trial procedures is what provides a clean and complete dataset for analysis.

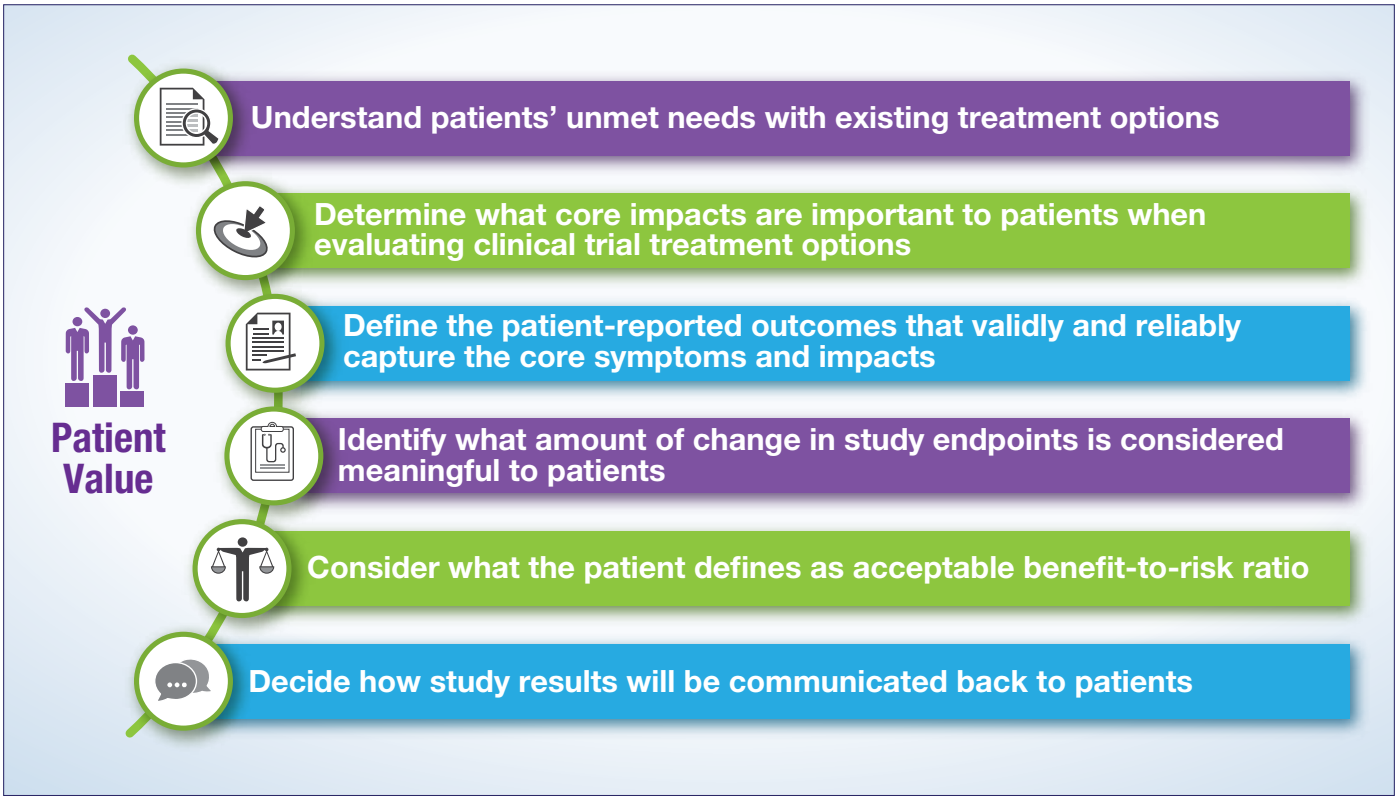
Every time a patient drops out of a study, it can cost up to $36,000 to add a new patient,[17] sometimes requiring the opening of new sites depending on dropout rates. The best way to ensure the engagement of patients is to support their experience, including understanding potential barriers (e.g., travel concerns, reimbursement, forgetting their appointments) and removing those barriers whenever possible. Patients want to feel valued and to know that sponsors understand that they are making a sacrifice to participate. Acknowledging and addressing those concerns can go a long way in keeping patients engaged in the trial by providing a patient-centric experience from protocol inception through to completion of the trial.

There are a number of ways to help engage and retain patients. Most importantly, listen to them. What do they need to keep them engaged? Providing transportation for patients who need it, sending reminders about upcoming appointments, providing rapid reimbursement of travel expenses demonstrate to patients that their concerns and needs are being heard, and their participation in the study is valued by the sponsor and community. Patients who truly feel that their participation will make a difference are much more likely to continue throughout the study. There are also unique and creative ways to engage and retain patients, such as study-specific apps that provide useful information easily (e.g., site and visit information, trial resources) and are often programmed to be fun and engaging to use. The use of an app gamifies the clinical trial experience by creating a virtual journey that softens a trial's clinical edge and creates a stronger bond between the patient and study. Ultimately, it is critical to always remember that the patients are the most important part of this process, and they should understand that this is acknowledged by everyone involved.

Building the Patient Value Story

In many countries and populations, patients now have more resources to learn about and engage in their own health care than ever before. Social media provides a means of social support and an opportunity to learn about patients' experiences with existing treatments. Patient advocacy organizations and medical associations have taken ownership of developing accurate, curated content so patients are more informed about their disease, the expectations as that disease progresses over time, and treatments options available to them. With increased access to health information, patients are more actively engaged in deciding when they want to start, stop, or

Figure 2. Developing a Patient-Focused Endpoint Strategy



change specific treatments. Research shows that actively participating in treatment decision-making results in a stronger likelihood of adherence to treatment.[18]

Informed Decisions Require INFORMATION

Patients need accurate, timely, and accessible information to make the best decision possible for them regarding their health care. This is where it is incumbent on those developing, regulating, and providing treatments to capture and deliver the information that demonstrates the value from the patient perspective. Building the patient value story involves designing an endpoint strategy that evaluates unmet needs, key impacts, and acceptable benefit-to-risk ratios as defined by patients *(Figure 2)*.

To understand patient perspectives on these key questions, patient insights can be gathered through qualitative, quantitative, and mixed methods. One-on-one interviews, focus groups, and social media analyses are ideal for an in-depth characterization of the patient experience. These types of data are rich in quality, but small in sample size and ideally suited for hypothesis generation in trying to understand the core issues that are most important to patients. Quantitative approaches, including surveys and patient questionnaires, are ideal for characterizing the patient experience in a broader sample. These methods are ideal for confirming the results of the qualitative methods, and evaluating differences in key subgroups (e.g., countries).

Communicating Study Results Back to Patients

Patients take on risk, give their time, and are inconvenienced when they participate in research studies. Yet in over 50% of cases, they never hear anything about the trial results.[19] They never know if they made a difference or what happened to the data that was collected. When results are available through clinicaltrials.gov, the content is not easy for patients to digest. For many published manuscripts, there are fees associated with obtaining the full-length articles. This does not foster transparency or encouragement for patients to participate in future trials. Developing and disseminating patient-friendly medical communications is a key unmet need in the field of medical product development.

The best way to communicate results to patients is to co-create study summaries with patients, physicians, and researchers so the message is both accurate, and communicated in a way that resonates with patients. In situations where results of clinical trials are not yet in the public domain, monthly or quarterly study summaries that provide information about the enrollment rates, educational information on the disease, or highlights of new studies can be very valuable to patients. Study protocols should ensure that the informed consent provides patients the opportunity to provide consent for the study investigators to share a study summary if they are interested in receiving this information.

Conclusion

By breaking down barriers and misconceptions about research, and educating patients and the public about clinical research, a community is created that is actively engaged in supporting medical product development. Working directly with this community to design protocols and solutions that make it convenient for patients to participate and stay engaged in the trial, recruitment and retention is facilitated. By designing endpoint strategies that measure patient-value and ensuring results are disseminated to patients, patients will be provided with the information they need when making the decision whether or not to start a new treatment. Collectively, these efforts result in a patient-centric trial, and ultimately, a patient-focused medical product. ■

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Market Access – Is Your Healthcare Communication and Data Dissemination Strategy the Missing Piece?

Planning Efficient and Effective Data Presentation, Dissemination, and Uptake

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Introduction

In the healthcare arena, market access traditionally refers to scaling the hurdles of payer reimbursement so that a product (drug or device) is included on insurance and hospital formularies. However, market access also depends upon healthcare providers having information to guide them in prescribing the product and patients having information to guide them in using the product. These two pieces of the market access puzzle are largely driven by healthcare communications such as journal manuscripts and medical information responses. Similar to the way payers need to understand the factors that differentiate a product for reimbursement purposes, healthcare providers need to understand how a product fits into their treatment armamentarium, and patients need to understand the proper use and suitability of a product for their needs.

Advances in technology have changed the way healthcare providers, payers, patients, and caregivers locate and


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interpret information. Providers and patients routinely turn to online sources for disease state and product information in their quest to learn about current and emerging treatment options. Since even a single online search may yield a variety of product information sources, it is critical that data generated about a product be developed, reported, and disseminated in a manner that provides the end user with reliable and consistent information in a format that is easy to understand. Data sources in the public domain that use outdated formats or provide incongruent information can ultimately hinder provider and patient access. If your product was researched today, would the information found be consistent across all sources and easy to understand? Would questions about product use be answered? Is the right information published in the right source and the right format to reach the right audience at the right time? These questions highlight the importance of having a strategic healthcare communication and data dissemination plan in place from the early stages of product development to address access factors for all stakeholders.

Healthcare Communications

What are the Current Communication Expectations of Healthcare Providers?

In today's healthcare environment, time is a highly valuable commodity for the provider. With minimal time to stay abreast of medical information, healthcare providers expect access to timely, relevant, and concise clinical information, as confirmed by the findings from a survey of 260 healthcare providers.[1] Data from this survey also showed that, when making treatment decisions, providers preferred sources of clinical information that were prospective studies, practice guidelines, and meta-analyses.[1] Increasingly, this information is being used to make clinical decisions at the point-of-care using mobile devices such as tablets or smartphones through internet-based, self-service portals.[2,3] Thus, the two critical pieces (e.g., medical information and manuscripts) used for healthcare communication and data dissemination should be compatible across different electronic devices and applications to complete the market access puzzle *(Figure 1)*.

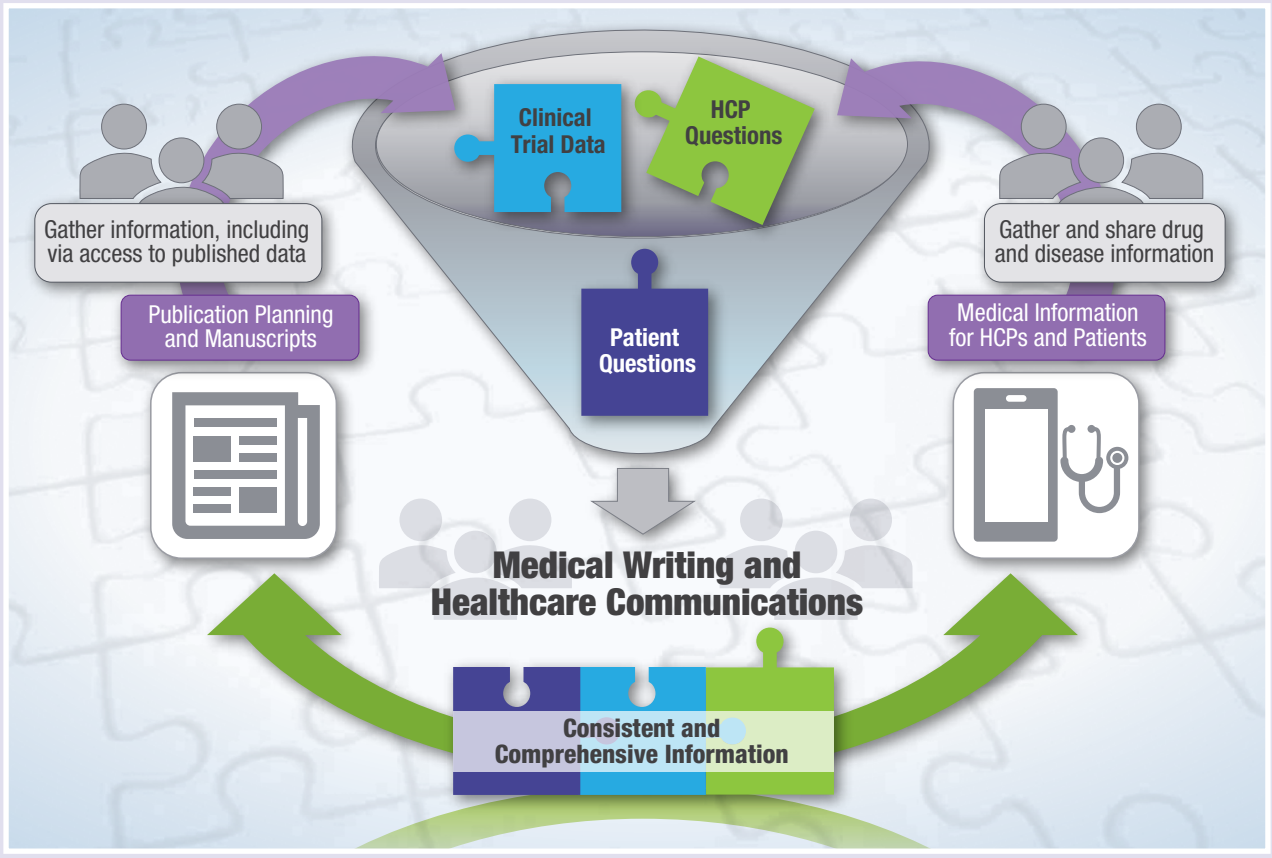
What Factors are Affecting the Communication of Medical Information?

Trends affecting the communication of medical information are associated with the following three factors.

Preference for shorter, focused responses

As medical information departments at pharmaceutical and biotechnology companies have evolved to meet the changing needs of healthcare providers, there has been a push to reduce content length. A recent survey of 25 pharmaceutical companies showed that, for the majority

Figure 1. Critical Pieces of the Healthcare Communication and Data Dissemination Plan



HCP=Healthcare Provider

of companies, the average length of standard medical information response documents is less than five pages.[4]

An evidence-based approach to content selection
In order to provide concise, relevant information, an evidence-based approach is critical and expected by providers. Healthcare providers and academic researchers prefer information developed from the strongest evidence[1] available on a topic and place greater trust in peer-reviewed[5] sources.

Global utilization of information and documents
Globalization of medical information capabilities is now common among pharmaceutical companies.[6] Ideally, this involves development of core content that provides consistent communication and messaging across the organization, but allows some local revision to meet the specific needs of each regional affiliate.[6,7] Thus, strategic development of core content with input from all stakeholders is necessary to ensure that all local regulatory and compliance needs are met.[6]

How has the Utilization of Data Evolved?

With technological advances, the rise of global internet access, and open-access journals, information is available to anyone with an internet connection; the result is a shift in the way data are used within the healthcare system.[8] Although a document may be intended for use by a specific audience, the ultimate end user on the internet may be anyone, including a provider, payer, patient, or caregiver. When feasible, a customer-centric approach for document development should be used, with the same data summarized in multiple documents, each for use by a specific targeted audience. With this approach, the information intended for payers focuses on product comparisons and health economics and outcomes data that are needed to differentiate products when making formulary decisions. Similarly, information intended for providers focuses on clinical outcomes, safety, and health economics and outcomes data that are used to make treatment decisions. For patients or caregivers, information focuses on proper use of drugs/devices, safety information, product comparisons, and disease-state education. Although a customer-centric approach to document development is still preferred,[7] use of the information by unintended audiences should be proactively considered during the document development and publication planning processes. Developing content that is designed for ease of reader uptake and adoption by payers, providers, and/or patients is one piece of the market access strategy.

The Art of Publication Planning

As technology continues to advance, sponsors must adapt and ensure that clear plans and structures are in place so data are disseminated in a timely and efficient manner.

What Factors Contribute to Creating a Strategic Publication Plan?

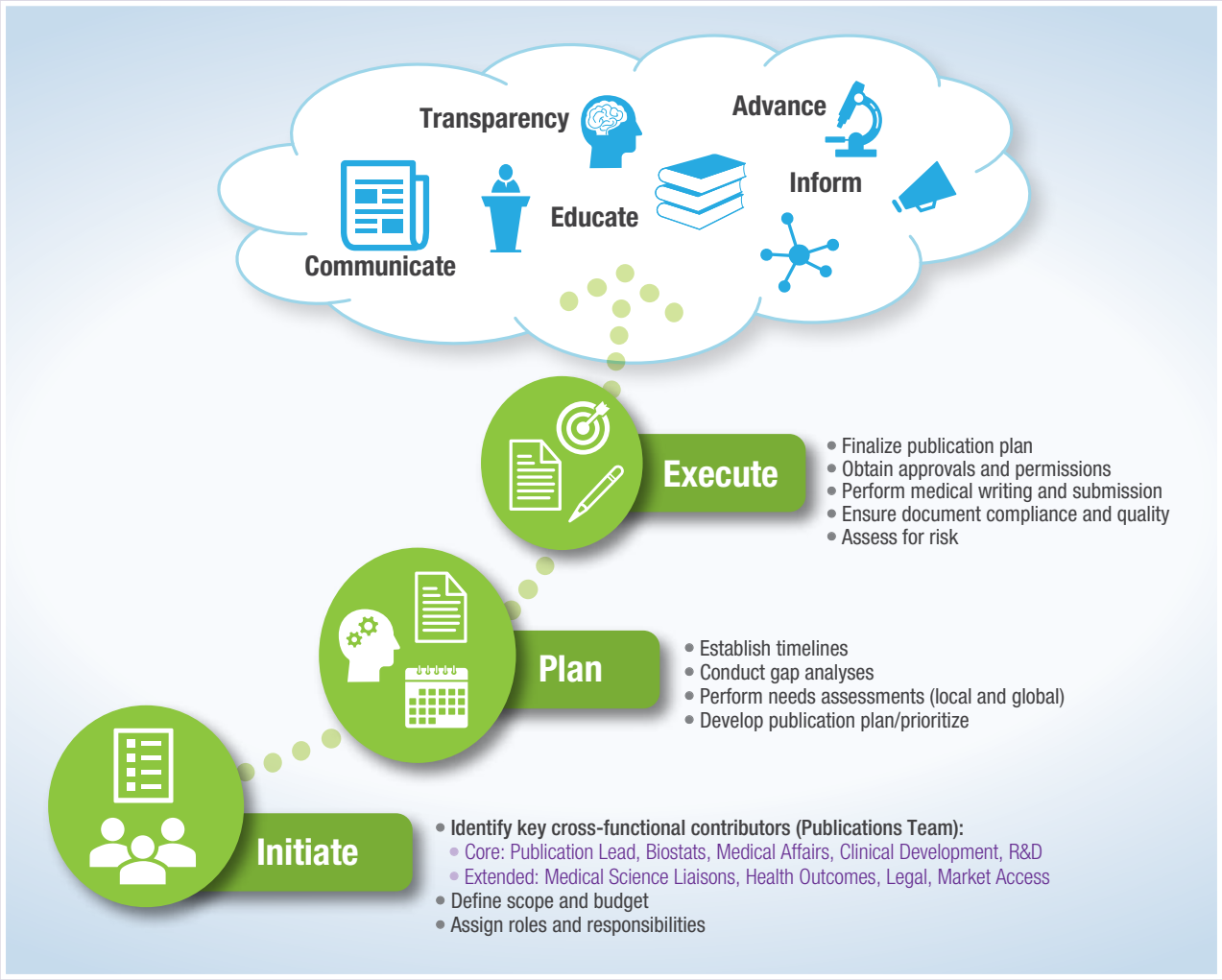
From the initial discussions at a small retreat organized by the Council of Biology Editors in 1998,[9] publication practice has evolved to include more definition and guidance. There are several publication-focused guidelines and best practices now available, including good publication practice (GPP3),[10] recommendations of the International Council of Medical Journal Editors (ICMJE),[10] and the Committee on Publication Ethics (COPE) guidelines,[11] that help guide sponsors on preparation and submission of manuscripts, authorship criteria, and ethical standards. There are also additional guidelines available based on specific study types, such as the Consolidated Standards of Reporting Trials (CONSORT), STrengthening the Reporting of OBservational studies in Epidemiology (STROBE), and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[10]

These guidelines support the premise that all clinical data – positive, neutral, or negative – should be published responsibly, timely, and ethically.[10] Transparency and ethical behavior related to publications has come to the forefront of good publication practice as the Office of the Inspector General of the U.S. Department of Health and Human Services has issued corporate integrity agreements to several pharmaceutical companies over the last 10 years because of questionable publication planning activities.[12] The increased demand for integrity, clarity on authorship, and dissemination of available clinical data over the last 20 years has contributed to a more regulated and systematic approach towards publication planning. Publication planning plays a significant role in the success of marketing a product because it serves as the foundation for conveying a consistent value story, from laying the foundation of the disease state all the way through to the post-marketing outcomes data. In this way, publication planning is a critical piece of the market access strategy.

What are the Key Elements of Publication Planning?

A well-developed publication plan *(Figure 2)* ensures that key cross-functional contributors are involved in the planning process, which can start as early as the proof-of-concept stage[13] or Phase II[14] of a clinical development program. Obtaining input from the various contributors helps identify and address data gaps while ensuring that scientific and clinical data are presented to the correct audience. It is also important to designate clear roles and responsibilities for the publication planning team members, which includes discussions about authorship and journal selection.[10] Journal selection alone involves multiple factors such as audience, circulation, indexing, impact factor, open access versus paid access, and time to publication. The importance of early planning cannot be overemphasized, as this clears the way for rapid communication of the data to the preselected outlet points once data become available.

Figure 2. Data Dissemination: Key Steps for Comprehensive Publication Planning



R&D=Research and Development

Publication tools such as gap analyses and needs assessments help the planning team prioritize the order and value of presenting critical background information, primary data, and secondary data. Other benefits that can be derived from a well-outlined plan are early external expert engagement, circumvention of redundancies, minimization of the risk of plagiarism in data presentation, and compliance with good documentation practices.[10] All of these factors, when addressed proactively, result in rapid and effective healthcare communications as part of the product life cycle support strategy.

Dissemination of data through a comprehensive publication plan can have an effect on current medical practices, lead to better treatment decisions, and better educate caregivers and patients.[10,14] As the number of publications continues to grow,[11] technology advances,[11] and more open-access data[15] become available, it is evident that sponsors must master the art of publication planning to better communicate product value stories not only to healthcare providers but also to payers, patients, and caregivers.

The Future of Communications

Patient centricity is driving change within the pharmaceutical industry, and this change includes the way data from clinical trials are presented, summarized, and disseminated to healthcare providers, patients, and/or caregivers.[16,17] Thanks to technological advances, patients and/or patient advocates are empowered to investigate medical needs and to bring their discoveries into dialogues with providers.[16,18] These interactions are affected by different mediums (e.g., infographics, plain language summaries) being used to communicate directly with patients and to aid providers as they educate themselves and their patients. Even though healthcare providers can assimilate knowledge equally well from text-based and infographic sources, many prefer infographics because of the overall reading experience (e.g., they are interesting and user-friendly).[19] Infographics can benefit patients by helping them understand and recall information they receive during interactions with healthcare providers.[20,21]

Why Infographics Over Text-Based Information?

- More interesting, use of color and graphics are engaging and innovative[22]
- User-friendly, easy to navigate and read[19]
- Increase attention and improve information recall[20]
- Improve comprehension and understanding (mainly for patients)[21,22]

Providers use the information they research and gather to educate themselves and inform their conversations with patients at the point-of-care,[1] with over 75% of patient consults including the use of a digital resource by the provider during the interaction.[2,23] Given this, it is important that the communication medium's format is compatible across different types of digital devices.

Because patients are central to and involved in their healthcare decisions, the availability of plain language summaries of clinical trials[18] and medical information letters written specifically for patients has recently increased. A public summary of a clinical trial, made available within one year of the trial ending, will soon be a requirement in Europe.[17] Dissemination of information generated during clinical trials is critical for providers and patients, as well as to ongoing and future research,[24] and scientists ultimately benefit as the reach of their research expands to a wider audience and has a greater impact within both the research and healthcare communities.[25] Since access to scientific publications has increased over time because of open-access policies, it is not surprising that scientific journals are listed among the top three resources patients seek out for information on diseases.[18] Access to information they can use and understand empowers patients and patient advocates to be active and important members of the healthcare decision-making team.[26]

Summary

As technology drives changes in product development, it also drives changes in communications and data dissemination. Broadened data access to providers and patients, through online sources, has created a need for intricately coordinated publication planning that anticipates the data points that will be relevant to these end users and presents them in a consistent manner.

In addition, formats for publishing data are evolving to keep pace with the way technology is changing readers' expectations for rapid access, brevity that does not compromise data integrity, and infographic presentations. In response to such changes, many industry-based medical information departments have begun adopting digital and social media channels to generate awareness, improve access, and provide relevant information in easy-to-use (practical) formats using these channels.[23] At least one biopharma company has kick-started a new mandatory open-access program for study manuscripts as a way to shorten time to publication and broaden access to product information to healthcare providers and patients.[15] From firsthand experience, Evidera is also aware of a sponsor who made the bold decision to initiate a program to provide medical information letters to patients, not just to providers, in an effort to provide patients with easy-to-understand product data.

These are a few examples of the ways in which healthcare communications and data dissemination are evolving to meet the dynamic needs of those who seek product data to inform patient care. These trends are expected to continue and will provide opportunities for both sponsors and medical writers to innovate in how we can partner together to meet the increasing demand for concise, consistent, and timely product information in an environment where data sources are plentiful. Thus, the delivery of consistent and comprehensive scientific and medical information requires a strategic plan that takes these factors into account from the early stages of product development. ■

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Pre-Approval Communication of Health Care Economic Information to U.S. Payers

Opening Doors for Patient Access

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The communication of health care economic information (HCEI) to payers in the United States (U.S.) **before** regulatory approval is an area of increasing interest and importance. Health care decision makers, specifically payers, formulary committees, etc., need to evaluate their plans and rates a year or more in advance in order to meet submission deadlines that often fall six to nine months before the start of a plan year.[1] Allowing manufacturers to share HCEI with payers prior to U.S. Food and Drug Administration (FDA) approval can lead to more accurate forecasting of budgets, more precise rates, and the possibility of more affordable patient access.[1] Historically, there have been a number of regulations regarding what can be discussed prior to FDA approval, but over the past 20 years there has been an effort to increase the amount of information that can be shared about a drug before its approval, most notably the Food and Drug Administration Modernization Act (FDAMA) Section 114 in 1997[2] and the FDA draft guidance on the communication of HCEI between drug and device manufacturers and formulary decision makers in 2017.[3]

FDA Draft Guidance on the Communication of Health Care Economic Information

This draft guidance on communication of HCEI, released in January 2017, aimed to clarify FDAMA Section 114, which was passed nearly 20 years earlier to facilitate HCEI exchange.[2] Because of the ambiguity surrounding FDAMA 114, few manufacturers took advantage of the act for fear of penalties associated with off-label promotion.[4] Given the need of formulary decision makers to review this information, the FDA draft guidance defines what constitutes HCEI, as well as who is considered an appropriate audience for such information *(Figure 1)*.[3] Examples of HCEI that manufacturers can communicate include budget impact models, health care utilization, and information on product pricing.[3, 4]

Format for Communication

One question that has been posed is whether or not a standardized format, such as one similar to the AMCP Format, should be used to communicate HCEI prior to FDA

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approval.[1] While this practice would probably benefit those familiar with the AMCP Format, it may not aid others who are unfamiliar with this framework.[1] However, starting with the AMCP Format should facilitate the development of a complete AMCP dossier when one is needed for post-approval decision making. In addition, the AMCP Format is updated on a regular basis, which allows it to adapt to reflect changing payer evidence needs.

The AMCP eDossier system

Currently, manufacturers may also provide HCEI to formulary decision makers through the AMCP eDossier system.[5] Using this system, manufacturers are notified when a formulary decision maker has requested information, and after directly authorizing the request, manufacturers may grant access to the dossier. However, manufacturers may not proactively distribute information to formulary decision makers or directly inform them that a dossier is available without first receiving an unsolicited request. Therefore, the AMCP eDossier System does not proactively inform payers that a particular dossier is available on the system.[6]

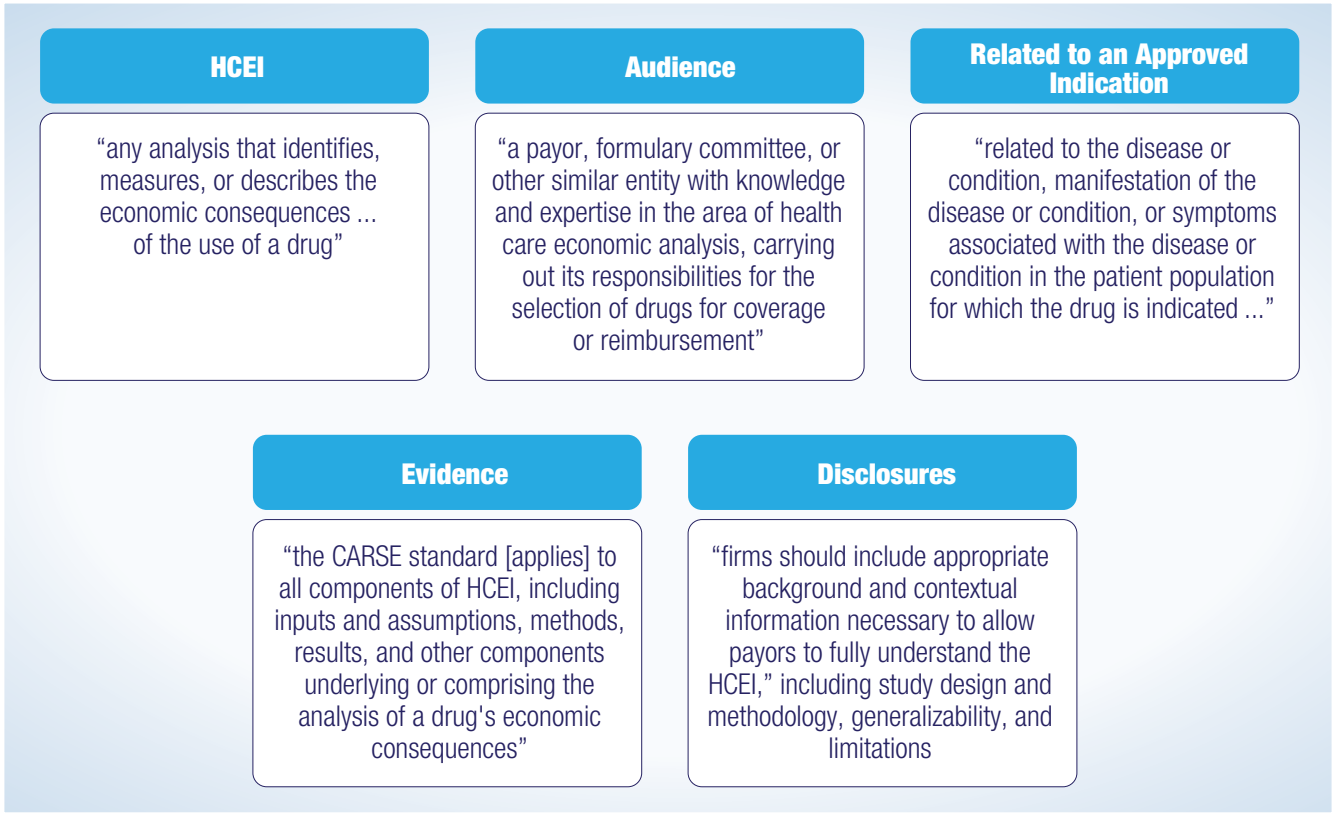
In accordance with version 4.0 of the AMCP Format, manufacturers may include dossier information on the eDossier system prior to FDA approval,[5] however, as noted above, payers must make an unsolicited request to receive the pre-approval dossier information.[6] In a November 2016 survey of payers currently using the eDossier system (N=172), more than 85% had been involved in requesting pre-approval information within the last year.[6] Payers in the same survey responded that the manufacturer response rate to information requests was better (40%) or the same (26%) for those using the eDossier system compared with manufacturers who did not.[6]

> Starting with the AMCP Format should facilitate the development of a complete AMCP dossier when one is needed for post-approval decision making.

In addition to providing another pathway through which manufacturers can share HCEI with payers, the AMCP eDossier system also:

- Allows manufacturers to verify that their dossier is available[6]
- Informs payers when new approvals occur and when updated labels are available[5]
- Provides Prescription Drug User Fee Act (PDUFA) dates to help keep payers aware of when different drugs might be obtaining approval[6]

Figure 1. FDA Draft Guidance on Manufacturer Communication with Payers, Formulary Committees, and Similar Entities



CARSE=Competent and Reliable Scientific Evidence; **HCEI**=Health Care Economic Information

SOURCE: FDA 2017[3]

A manufacturer using the AMCP eDossier system also knows which payers have requested the dossier because the manufacturer is the one who grants access to the payer's unsolicited request.[6] In addition, payers can designate a timeframe during which they will need the information (e.g., during the next three months).[6] Designating a timeframe allows payers to request pre-approval and post-approval dossier information even if an AMCP dossier is not available (e.g., sometimes an AMCP dossier is not available when a drug receives approval).[6]

The Pharmaceutical Information Exchange (PIE) Act

In April 2017, the Pharmaceutical Information Exchange (PIE) Act (HR 2026) was introduced to the House of Representatives by Representative Brett Guthrie (R-KY). The PIE Act would provide for earlier exchange of HCEI, theoretically leading to quicker and improved patient access following FDA approval. Unlike the current system of HCEI, in which an unsolicited request from a formulary decision maker is required to initiate the exchange, HR 2026 provides for the proactive exchange of HCEI.[7] Formulary decision makers have consistently called for access to pipeline information 12 to 18 months prior to approval to accurately forecast the following year's budget and premiums.[6] HR 2026 is currently under review by the House Energy and Commerce Committee, but if it does eventually become a law, it has the potential to empower formulary decision makers to conduct quicker and more accurate assessments of drugs for their members.

Conclusion

Currently, the U.S. health care system is still evaluating the optimal way in which to use HCEI to accurately manage health care costs, but recent regulation and guidance have been instrumental in making improvements to the system. There is increased communication between the key stakeholders – drug manufacturers, the FDA, and payers – and continuing efforts to improve the system in a safe and structured manner. With the FDA draft guidance allowing some communication of HCEI to payers prior to regulatory approval, and the potential for even greater expansion of this communication through HR 2026, the U.S. could see improved formulary decisions, budget forecasting, and precision in rates, all translating to better patient access to medical treatments.

It is imperative that biopharmaceutical companies continue the dialogue with the FDA, payers, and other stakeholders (such as AMCP) to keep the momentum moving forward on this issue. With the changing landscape of health care and the shifting emphasis to value-based pricing, early approval of treatments to meet unmet need, and personalized medicine, the pre-approval communication of HCEI will only become more important to payers to adequately plan for patient access to the treatments they need. ■

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Is Real-World Evidence Needed in Comparative Effectiveness Research? Yes, But…

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Real-world evidence (RWE) is increasingly recognized as a key source of information and insight in conducting comparative effectiveness research (CER). This is particularly true in the context of demonstrating product value through comparative effectiveness assessment (CEA) involved in health technology assessment (HTA). However, the disparate nature of RWE coupled with the lack of definitive guidance on its use means there can be confusion, scepticism, or even distrust about its inclusion in attempts to compare treatments outside the setting of head-to-head interventional studies. This article discusses these concerns and how they might be addressed.

Why RWE?

CER is an analytical process to demonstrate "the extent to which an intervention does more good than when compared to one or more intervention alternatives for achieving the desired results and when provided under routine setting of health care practice"[1] (i.e., in the real-world setting). The main drivers for the use of RWE in such analyses are circumstances in which randomized controlled trials (RCTs) are not feasible or have limitations that leave key gaps in knowledge. Such data, in theory, can either supplement, or compensate for the absence of, relevant RCTs and may thereby provide a broader perspective of a product's effects. Specifically, while RCTs seek to answer the question "Can this product work in a highly selective, relatively homogeneous population?," RWE might help provide the answer to "Does this product work for a heterogeneous group of patients that would be found in a typical everyday clinical setting?" *(Figure 1)*.

However, deciding whether, where, and how to employ RWE in this way is complicated by the lack of definitive conceptual frameworks, accepted guidance, and collective, longstanding experience associated with the generation and use of RCT data. Indeed, there is even a lack of standardization and agreement on what is the "right" term to define data that captures patients' experiences of receiving a technology under real-life conditions and what evidence should be included under this umbrella. The terms RWE, real-world data (RWD), and "big data" are often used interchangeably to describe everything from patient-level data collected in electronic health records (EHRs) from insurers or governmental health programs, to patient registries, to surveys and information gathered through health "apps" and other connected devices. Against this background, it is not surprising that even those who recognize the potential benefits of RWE in CER may be daunted by the practicalities of their use.

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What are the Main Challenges for RWE in CER?

The biggest obstacles in efforts to use RWE in CER relate to developing a valid and reliable process for data collection and analysis that will provide unbiased estimates of a technology's effectiveness compared to standard clinical care. Meeting this objective is clearly paramount where data on the product will be scrutinized by HTA bodies or payers seeking to decide whether reimbursement is justified.

Until recently, however, a lack of trust related to inherent limitations of RWE has hindered the uptake of such data into HTA/payer decision-making. These doubts specifically include worries about the quality of both the sources and collection of RWE, patient selection processes, and publication bias in reporting of the data. Consequently, CER continues to be heavily based on the methodological interpretation of RCT evidence and evaluating the level of "uncertainty" produced by that type of evidence.[2-4] In this context, use of RWE to demonstrate a technology's value in reimbursement processes has been restricted to supplementing sparse RCT evidence or providing information on epidemiology and burden of disease (humanistic and economic) for pharmacoeconomic analysis.

How Can the Challenges be Overcome?

Ways of increasing the validity of RWE in CER include appropriate choices between potential data sources, transparency in data collection, and the use of available methods for addressing limitations related to the lack of randomization of treatment allocation. The following diagram summarizes the most widely proposed approaches that can be considered by investigators and drug companies when RWE is needed to help define a technology's relative effectiveness *(Figure 2)*. These

Figure 1. Lack of Trust and Limited RWE in Initial Reimbursement Decisions

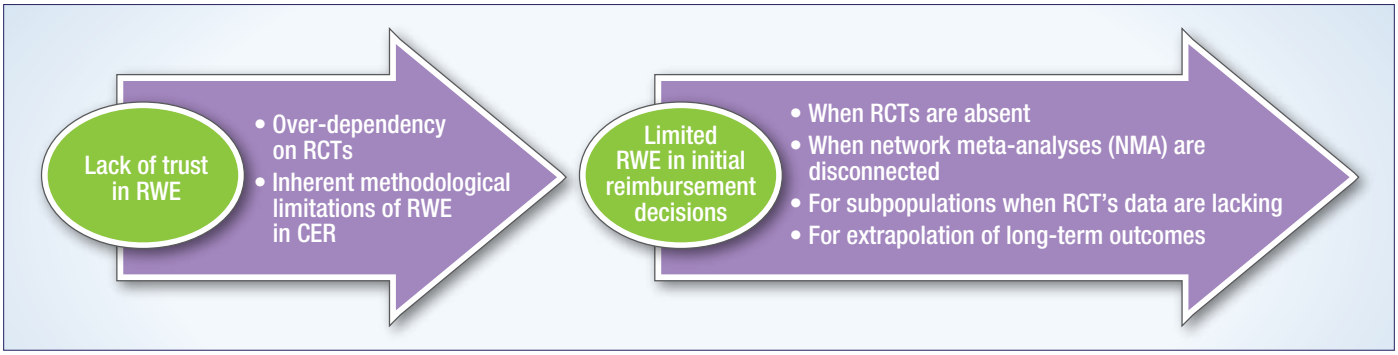
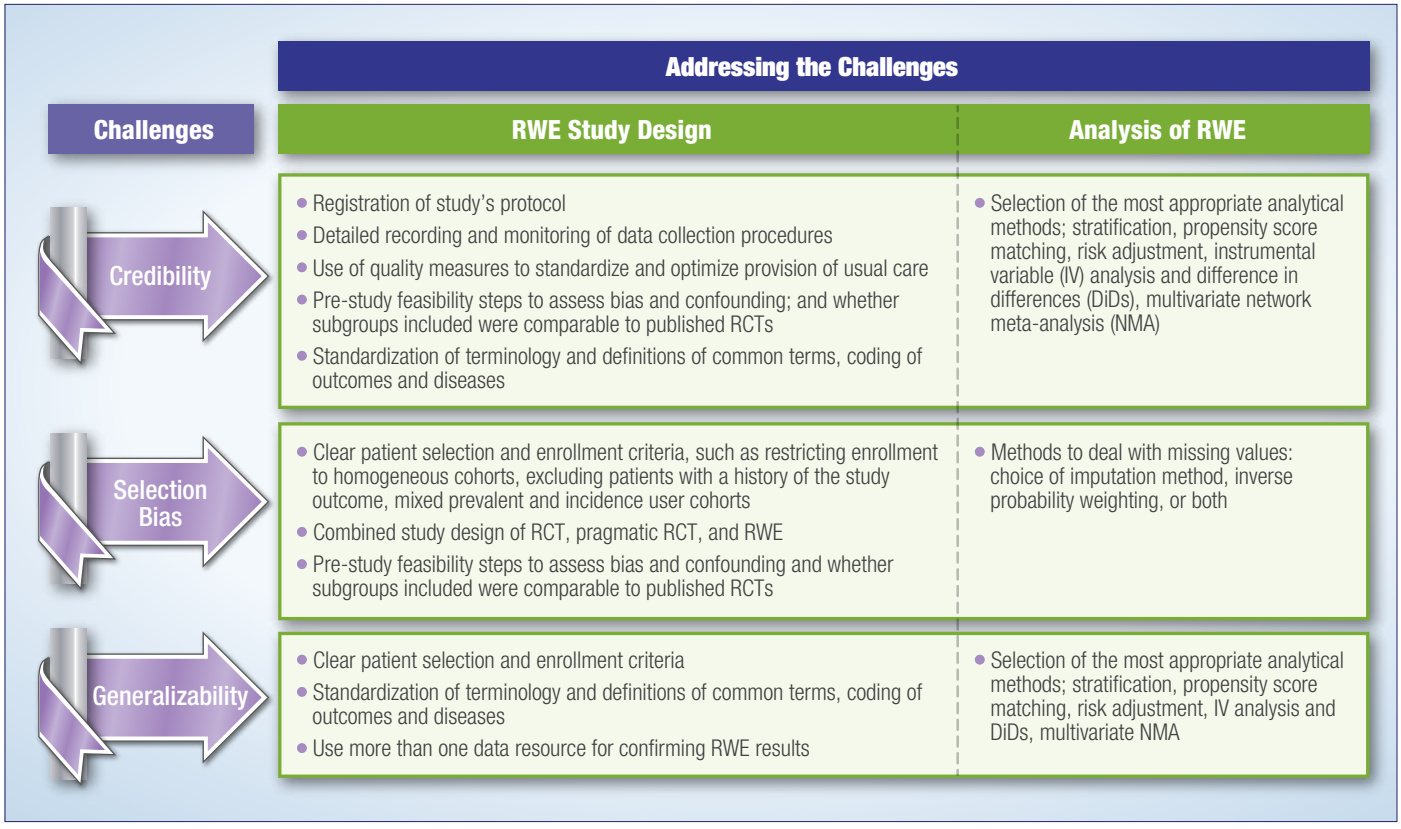
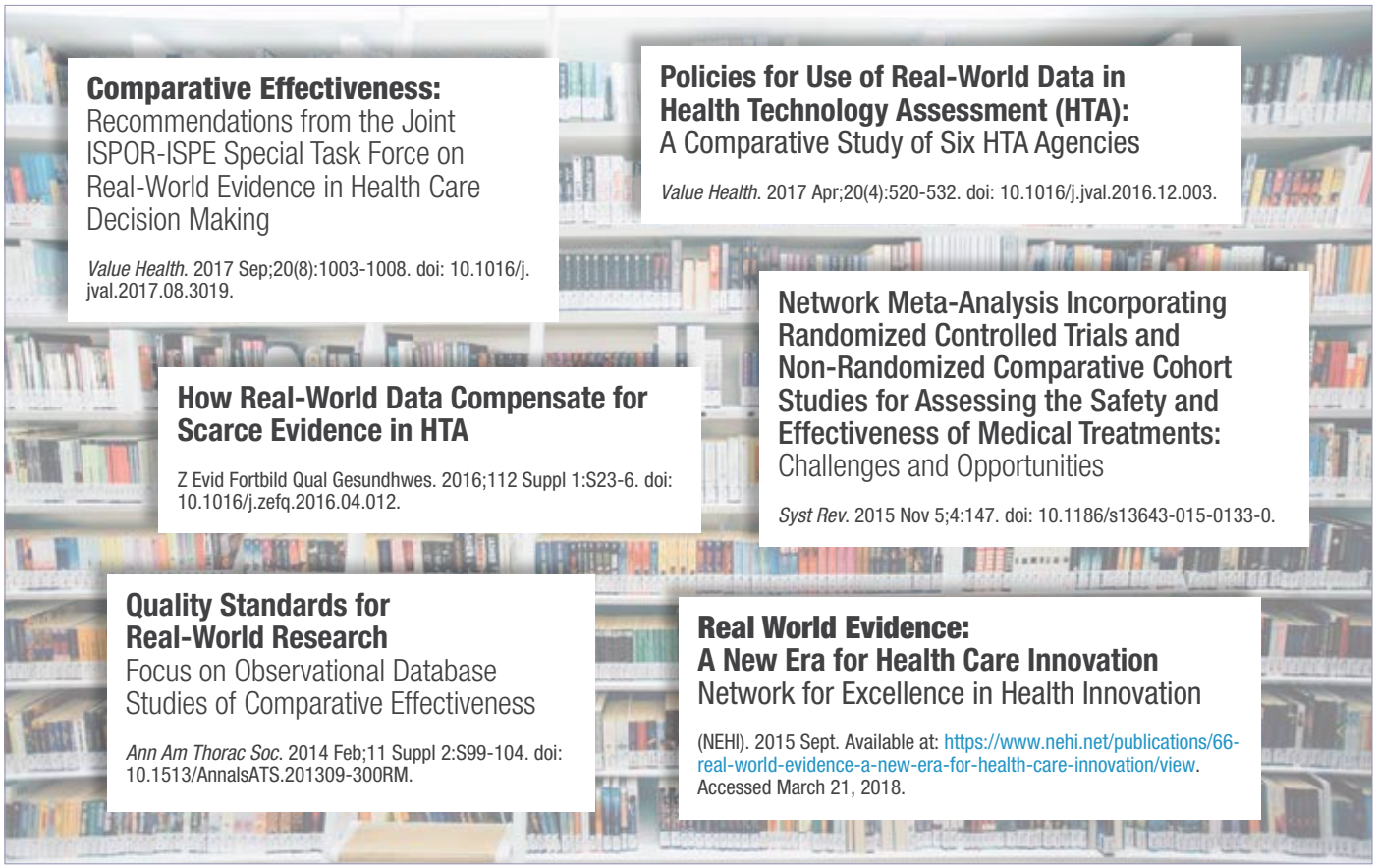


Figure 2. How Can the Challenges be Overcome?



Samples of the Proliferation of RWE for CER Publications in Recent Years



solutions target the three main challenges related to the interpretation of RWE findings in CER: selection bias; credibility of the data-collection process; and, generalizability of findings to the population for whom the technology is intended.

What are the Current Place and Potential of RWE in CER for Reimbursement Decision-Making?

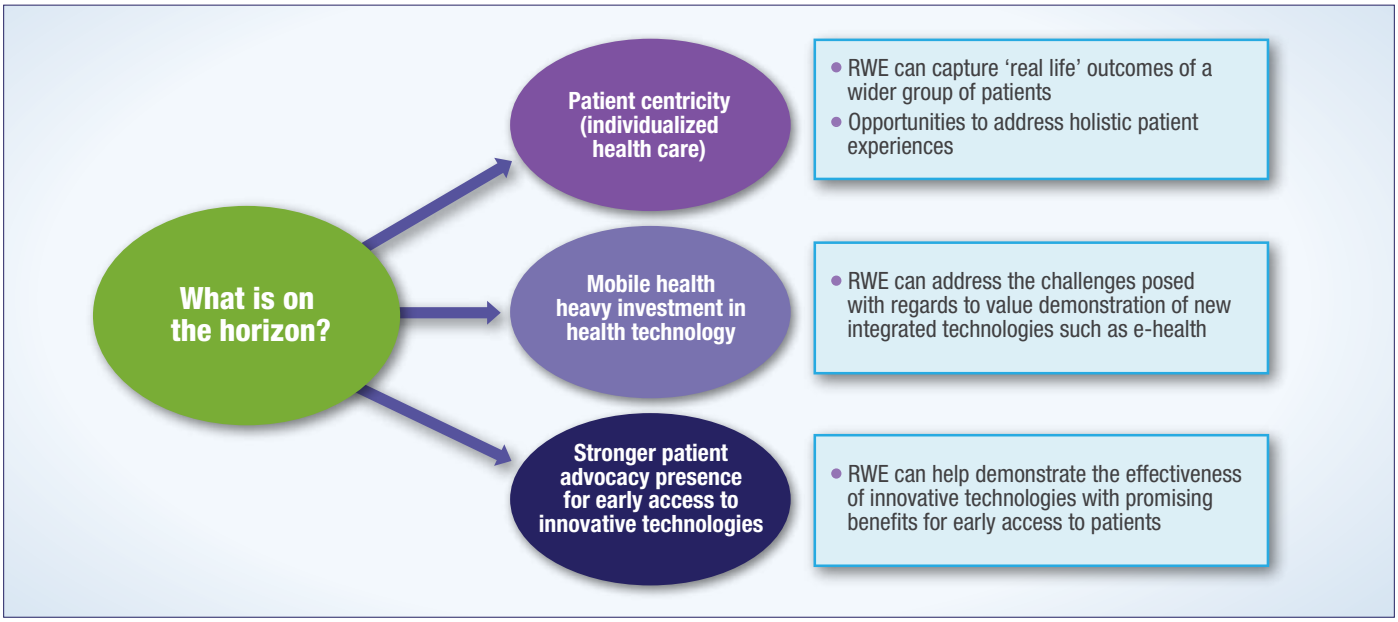
It is important to note that the potential for integrating RWE in health care decision-making is not new. For example, the first International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Real-World Data Task Force Report, published in 2007, proposed a framework for use of RWE in health coverage and payment decisions and emphasized the role of estimates of effectiveness rather than efficacy in a variety of typical practice settings.[5]

What has Changed in Recent Years to Increase the Spotlight on RWE?

Globally, there is a movement to capitalize on the potential for RWE in CER.

- In Europe, the Innovative Medicines Initiative GetReal Consortium (IMI-GetReal) has been a major influence in promoting close collaboration between different stakeholders (including academics, policy makers, and pharmaceutical companies) to investigate policies and methodologies for the collection and use of RWE in drug development and assessment. Furthermore, the RWE-navigator (https://rwe-navigator.eu/) – an output of this initiative – now serves as an educational and guidance tool to enable users to understand issues around demonstrating relative effectiveness of a new technology, therefore enabling the identification of the best study designs or analytical approaches to address these issues.
- In the U.S., the 21st Century Cures Act[6] stated the need for the Food and Drug Administration to develop a regulatory framework to evaluate RWE potential to support approval of new indications for approved drugs or satisfy post-approval study requirements.
- Recent changes in the market access landscape, with shifts in pharma health economic and outcomes research (HEOR) activities and HTA requirements, have facilitated the increased role for RWE in CER. In addition, the requirement to incorporate RWE into CER is likely to grow with the transformative possibilities of mobile health,[7] the changes in the conceptualization and operationalization of health care (including greater emphasis on individualized management and the patient voice in decision-making), and the push for earlier introduction of innovative technologies into the market[8,9] (such as Early Access Management Schemes) *(Figure 3)*.

Figure 3. The Increasing Role of RWE



Conclusion

Although the assessment of product value will probably still be largely determined by efficacy in "hard" clinical and/or cost-effectiveness outcomes such as mortality and quality-adjusted life years (QALYS), the current landscape clearly indicates a growing interest in using RWE throughout the drug development and assessment process. New trends in health technology assessment are expected to place a higher value on the use of RWE in CER and/or in supporting technology in initial reimbursement or post-marketing assessments. Once seen as the lesser to so-called "gold standard" evidence, RWE increasingly will be seen as a must-have in CER. ■

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Market Access Policy
EU HTA - Looking Back to Better See Ahead

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On 1 February 2018, European Union (EU) member states received a draft regulation from the European Commission setting out the creation of a single, mandatory system for clinical health technology assessments. The intention is for this system to be introduced beginning March 2019 with provisions allowing for a three-year transition period. The draft regulation includes a request for adoption within eight weeks, by 3 April 2018.[1] The primary objective of this draft regulation is to allow expedited patient access to new, essential medicines. While the clinical benefit will be assessed centrally and member states are required to adopt decisions, health economic assessments and pricing and reimbursement decisions will remain within the individual member states. The scope of the draft regulation may be far more reaching than many health technology assessment (HTA) stakeholders anticipated, or indeed, would support.

There should be little surprise considering the activities of the past five to seven years. Before the release of the 1 February regulation, the European Commission announced the 2011 decision on the application of patients' rights in cross-border health care[2]; the 2013 decision on establishing a transparent network of national authorities and bodies in health technology assessment[3]; and several multiannual work programmes on HTA collaboration, such as 2014-2015 and 2016-2020,[4] all of which indicated a move towards a single centralised system.

Historically, member states, and in particular Germany, have justified specific and distinct approaches to value and benefit assessment of new treatments in the form of an HTA as necessary to align with their health system values, health service organisation, and standards of care.[5]

Following the first whispers from the European Commission of the possible introduction of an EU-wide HTA collaboration and assessment in 2011, the topic of health became increasingly relevant to individual EU members states, particularly with respect to general elections.[6-8] As a result, over the last 12 months many EU member states introduced considerable changes to their HTA and pricing and reimbursement systems in response to demands from the electorate in their country.

However, apart from the electorate, national HTA changes need to take into account the greater EU HTA on clinical efficacy benefit to make a concerted effort worthwhile. Policy changes in 2017 and 2018 across all member states should focus on preparing for 1 March 2019 and align national processes to the EU HTA initiative. March 2019 will be here faster than we think, so a key question is how well adjusted are these latest rounds of national HTA changes with the 1 February draft regulation on EU HTA?

To help answer this question, we have looked at selected HTA changes implemented in 2017 in several EU member states and assessed the level of alignment to the broad framework set out in the 1 February draft regulation on EU HTA.

Based on the 1 February draft regulation, the European Commission envisage a single EU system for clinical HTAs, with mandatory cooperation between member states on clinical HTA assessments after 2019. The mandatory

Alignment with 1 February Draft Regulation on EU HTA

● = Good alignment ● = Unclear alignment or further adjustments will likely be needed ● = Poor alignment

France

Key Developments in 2017		Implication on National Price and Reimbursement	Alignment
SMR and ASMR Reassessments	• Some SMR and ASMR ratings were reassessed based on real-world evidence (RWE) data • All the reassessments resulted in a downgrading of the product's rating compared with the product's initial rating • Changes in initial price, as a result of the lower ratings, will follow in 2018	• Trend to proactively manage health care resources based on actual value in real-world (i.e., non-clinical trial) setting	
Updates in HTA Pathways	• Introduction of joint commissioning between TC/ CNEDiMTS/CEESP to evaluate clinical and economic criteria simultaneously	• Pathway becoming more health economics driven • Most important use is expected for joined assessments of economic and clinical value by TC and CEESP	
New Regulations on Interchangeability of Biosimilars	• Interchangeability between biologics and biosimilars at any time in the pathway • ARS have been asked by the Ministry of Health to encourage biosimilars use	• Likely to lead to a shift in the price-focused commercial strategy of current biologics	
New Additional Criteria for CEPS Price Referencing	• External price referencing to be applied regardless of ASMR • Use of net purchase price of competitor products • Use of net treatment cost if concomitant or sequential use with other drugs	• Increase pressure in price negotiations • End of patent and/or first generic entrant can lead to renegotiation of price	
Introduction of Chronic Patient Experience as Part of Drug Evaluation	• Patient participation and experiences will now form part of the clinical evaluation for HAS decision-making • Currently, patient involvement processes are in trial period, but a formalised process is expected	• Influence of patient perspective to increase in the future	

ARS=Regional Health Agencies (Agence Regionald e Sante)
ASMR=Improvement of Medical Benefit (Amélioration du Service Médical Rendu)
CEESP=Commission Evaluation Economique et de Santé Publique
CEPS=Economic Committee of Health Products (Comité Economique des Produits de Santé)
CNEDiMTS=Commission Nationale d'Evaluation des Dispositifs Médicaux et des Technologies de Santé
HAS=National Authority for Health (Haute Autorité de Santé)
SMR=Medical Benefit (Service Medical Rendu)
TC=Transparency Committee (Commission de la Transparence)

Germany

Key Developments in 2017		Implication on National Price and Reimbursement	Alignment
Changes Influencing Price Negotiations	• Price moratorium was extended to 2022 for drugs not subject to a fixed price reference group • Flexibility has been introduced to price negotiations when the comparator is a very low-cost treatment • Reference price groups can no longer only include branded drugs	• Price pressure increased through increased scope for manufacturers to negotiate the most appropriate price comparator within the indication • Pharmacy profit margins will be impacted with loss of hospital contracts	🟢
Process Changes	• Manufacturers can start AMNOG re-evaluation after one year (as opposed to 15 months under prior regulation) • Drugs launched before 2011 and still under patent protection can be assessed under AMNOG, if manufacturer applies for new indication	• Opportunity for faster re-evaluation if new evidence is anticipated or becomes available to achieve a more a positive outcome	🔴
Selected Method Changes (per the updated IQWiG methods paper – version 5)[9]	• Subgroup analyses are now only considered if at least 10 events occurred in the subgroup and the significance level has been lowered to α=0.05 • New Methods paper provides guidance on evidence generation, information searches, and expectations to supply RCT data for high risk therapy methods and devices • Evidence transfer between populations and subgroups needed to better accommodate lesser explored patient groups (e.g., children)	• Adjustment to subgroup analyses will be relevant for trials in smaller populations (e.g., orphan drugs) • IQWiG will no longer conduct a benefit assessment for small groups where the manufacturer previously could have reached a positive benefit outcome	🔴

IQWiG=Institute for Quality and Efficiency in Health Care

Italy

Key Developments in 2017		Implication on National Price and Reimbursement	Alignment
Changes to Drug Expenditure Governance Rules Under 2017 Finance Act	• Reduction of industry payback obligations for budget overruns • Innovative drug sales exempt from payback obligations • Dedicated funding of €1 billion a year for drugs designated as innovative; funding split equally between oncology and non-oncology	• These measures represent early moves towards reform of the pharmaceutical governance system, notably the payback burden currently shouldered by industry • Regions have new responsibility to fund drugs when spending exceeds the innovation budget	🟢
AIFA's New Criteria for Innovative Drugs	• Innovative medicines are identified based on unmet need, added benefit and strength of evidence. • Assessments will consider the quality of evidence, therapeutic need, and additional therapeutic value • Final ratings will consider:	• Innovative drug status provides commercial and access advantages, including mandatory listing across regions and reimbursement from dedicated innovation budgets • It is critical to demonstrate innovation along the defined criteria in order to receive these advantages! • Special provisions exist for orphan/ rare treatments where unmet need is high, but evidence is limited • Limited transparency around decision making remains a challenge – to date, no assessments have been made public and decision drivers in individual assessments are not well defined	🔴

Therapeutic Need	Added Therapeutic Value	Quality of Evidence		Outcome Rating	Impact
Major/ Important	Major/ Important	High	=	Innovative	• Automatic listing in regional formularies • Reimbursed through innovation fund • Exemption from payback liabilities • Valid for 3 years
Intermediate situations will be evaluated on a case by case basis considering the relative weight of the individual factors considered			=	Potentially Innovative	• Automatic listing in regional formularies • Valid for 1.5 years
Low/None	Low/None	Low/ Very Low	=	Not Innovative	• Reimbursed at or below price of existing treatments or not reimbursed (class C)

AIFA=L'Agenzia Italiana del Farmaco (The Italian Medicines Agency)
Sources: Legge di Bilancio 2017 (Finance Act 2017), Gazzetta Ufficiale 21/12/2016; Determina AIFA 1535/2017 Criteri per la classificazione dei farmaci innovativi e dei farmaci oncologici innovativi (18/09/2017)

Alignment with 1 February Draft Regulation on EU HTA

🟢 = Good alignment 🟡 = Unclear alignment or further adjustments will likely be needed 🔴 = Poor alignment

England

Key Developments in 2017		Implications on National Price and Reimbursement	Alignment
Fast Track NICE Technology Appraisal Process for Promising Technologies Falling Below £10,000 per QALY	**Conditions for Fast Track Assessment (FTA)** • Company's base-case ICER is less than £10,000 per QALY gained • Most plausible ICER likely to be less than £20,000 per QALY gained; highly unlikely to be greater than £30,000 per QALY gained • NICE is satisfied the proposed place in therapy is appropriate • Sufficient information exists to make recommendations through an FTA • Uncertainties in the evidence and consequences of decision error are manageable	• For new drugs that are highly likely to be cost-effective, a fast track appraisal will result in a NICE recommendation within 32 weeks of submission, compared with the standard 43 weeks • This is intended to drive rapid reimbursement and uptake of highly cost-effective innovative technologies	🔴
Budget Impact Threshold of £20 Million Per Annum Will Result in Commercial Agreement With NHS England	• NHS is committed to providing the 'most effective, fair, and sustainable use of finite resources' • Increased focus on the management of the introduction of cost-effective therapies that have a significant impact on the NHS budget • NICE and NHS England have introduced a 'budget impact test' to assess the level of the affordability challenge that new drugs present • NHS England will review the policy in 2020 to determine impact on access and uptake for new drugs and any potential policy adjustments	• For drugs with a predicted net budget impact of ≥£20m per year, in any of the first three years of use, a commercial discussion will be triggered with NHS England (with a risk of delayed access without an agreement) • Discussion will include ways to introduce the product that is acceptable to both the company and NHS England; may involve pricing or model options for how to pay for the product • If agreement is not reached, NHS England can apply to NICE to allow phased introduction of the product over period longer than the standard 90 days	🔴
NHS England Will Automatically Fund Highly Specialized Technologies (HST) Up to £100,000 per QALY	• HSTs with ICER above £100,000 per QALY can also be considered for funding • Funding from routine NHS commissioning will be made available to medicines for very rare ultra-orphan diseases (assessed by the NICE HST programme) with an ICER up to £100,000/QALY	• For HSTs, large QALY gains are common. This suggests the proposed weights may be a regular consideration for appraisals • Estimating the lifetime QALY gain requires extrapolation from sparse data. This is more likely to rely on mortality rather than morbidity, **implying that patients must be young enough to accrue sufficient QALYs**	🔴
Establishment of 4 Regional Medicines Optimisation Committees (RMOCs) in England	• The 4 RMOCs (London, South, North, Midlands/East of England) will operate as a single, strategic medicines optimization system for England • Participants will include decision makers, clinicians, patients and public representatives • RMOC recommendations are advisory and do not affect statutory legal responsibilities and duties of the NHS	• RMOCs will coordinate evaluations and make recommendations to guide the adoption of new medicines that are not scheduled for review by NICE	🔴

ICER=Incremental Cost-Effectiveness Ratio
NHS=National Health Service
NICE=National Institute for Health and Care Excellence
QALY=Quality-Adjusted Life Year
RMCO=Regional Medicines Optimisation Committees

Sources:
https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/process-guide-addendum-fast-track.pdf
https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-highly-specialised-technologies-guidance
https://www.england.nhs.uk/wp-content/uploads/2017/04/regional-medicines-optimisation-committees-operating-model.pdf

joint assessment will be limited to examining the clinical evidence and the comparative efficacy with the final recommendations binding on all member states. There would be no option to re-evaluate these assessments at the national level. Pricing and reimbursement (P&R) decisions, based on these joint assessments, would remain the responsibility of national-level governments as would the assessment of health economic evidence. At the same time, member states have been introducing changes and innovations to their HTA and P&R systems, some of which appear to go against this EU strategy.

This raises the question of the level of policy preparedness and alignment that exists for both the EU members and the EU Commission. Therefore, to allow the transformation of this draft regulation to become a policy decision providing the greatest benefit to the patient, fundamental questions still need to be addressed, including:

- Will an EU HTA assessment of clinical benefit reduce payer uncertainty in member states with respect to P&R decision making when measured by national standards of evidence needs for P&R?
- How will real-world evidence feature in EU HTA assessments or at the national member states level or the local level? This is particularly important as many high technology treatments may not be able to develop all the data required for comparative efficacy assessments.
- How many adjustments will be required for the national health economic assessments?
- How are patients intended to contribute to the EU HTA clinical benefit assessments?
- How will differences in standard-of-care and patient pathways across member states be considered in comparative efficacy assessments?
- How do price building processes within the member states need to be adjusted if comparative efficacy may not allow for value ratings and clinical benefit re-assessments are not allowed at individual member state level?

Hence, policy discussions must take place across all member states and the European Commission as soon as possible to address these key questions to ensure that the intended patient benefit is appropriately introduced. ■

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The First Re-Evaluations in France Based on Real-World Evidence

Another Good Example of Starting with the End in Mind

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Among the many possible uses of real-world evidence (RWE) by pricing and access decision-makers, one is in re-evaluation of initial health technology assessment (HTA) decisions. France, which leverages RWE among other data sources in its HTA reassessments, presents an interesting case to consider RWE's role in such reviews. There were three products reassessed by the French National Authority for Health (HAS) in 2017 for which the Transparency Committee (TC) considered RWE in the reassessment. Table 1 summarizes these three cases.

Given the relative frequency with which Temporary Authorization for Use (ATU) data are considered in reassessments, a key challenge concerns the robustness of ATU data – or lack thereof. For instance, the ATU for Tagrisso suffered from a significant missing data problem. Of the 408 patients in the ATU, treatment evaluation forms were only received for 151. Of these, there was no radiological tumor evaluation for 16 patients, and there were "not assessable" or unspecified results for 8 more patients, leaving only 127 pieces of data to evaluate. The Transparency Commission does not assess the remaining data in percentage terms in its opinion, but rather only cites absolute numbers of the 127 who had partial or complete response, stabilization of disease, or disease progression. It is difficult to see how the HTA body can make good use of such data, which may suffer from a multitude of problems (e.g., selection bias), when considered alongside appropriately powered, well-designed clinical trials, even if the external validity of the ATU data is high by virtue of being "real-world" data.

The case of Kolbam underscores the robustness problem in cases of extremely rare diseases – there may simply be too few patients in the entire country who can benefit from a therapy to build up a robust ATU dataset for consideration by the HTA body.

The case of Myozyme shows that drug registries need to be carefully designed with the HTA body's key question in mind – in this case, whether the drug slows disease progression in late-onset Pompe disease. Failing that, the registry data may not support the reassessment in one direction or the other, as in this case.

Another challenge, exemplified by the Yervoy case, is the potential obsolescence of the RWE in quickly evolving categories. It is rare to see such a wealth of RWE considered in a reassessment, which in this case included:

- post-registrational study set up at the request of CEPS re: survival, safety, and quality of life, using data from MELBASE, a prospective, observational, non-comparative cohort study promoted by Assistance Publique – Hôpitaux de Paris

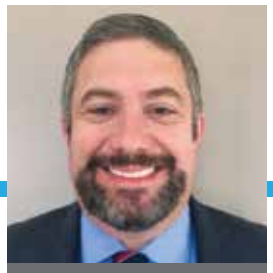

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Table 1. Snapshot of RWE in French HTA Reassessments, 2017

Drug	Indication	Orphan Status	RWE Included in Reassessment	Date of Original Decision to Reimburse & Ratings	Date of Re-Assessment Based on RWE	Impact of Reassessment	Key Issues re: RWE Raised in Opinion
Kolbam (cholic acid)	Lifelong treatment of adults and children who cannot produce enough primary bile acids due to genetic abnormalities that result in lack of sterol 27-hydroxylase, 2-methylacyl-CoA racemase, or cholesterol 7a-hydroxylase	Orphan	ATU (i.e., "temporary authorization for use," aka compassionate use) data	• December 17, 2014[1]: decision on SMR delayed until ATU data are available for analysis	September 13, 2017[2]	SMR insufficient (i.e., no longer reimbursed)	Weak RWE base – in the absence of clinical data, the TC noted it could not make a risk/benefit assessment and therefore determined that the molecule is not to the benefit of health service / patients
Myozyme (alglucosidase alpha)	Long-term enzyme replacement therapy in patients with Pompe disease (acid alpha-glucosidase deficiency)	Orphan	RWE data collected by CSEVR	• September 20, 2006: in juvenile onset disease, SMR major, ASMR II; in late onset disease, SMR insufficient[6] • June 16TH, 2010: in late onset disease, SMR low, ASMR IV[7] • January 13, 2013: no change in late onset disease[8]	October 18, 2017[9]	ASMR downgraded from II to III for juvenile onset disease	Long-term registry data for patients with late-onset disease only confirm that the disease continues to progress in treated patients, not whether the drug slows the rate of progression
Yervoy (ipilimumab)	Advanced (unresectable or metastatic) melanoma	Not orphan	Various, including post-registration study commissioned by CEPS, retrospective studies in U.S. setting, etc.	• December 14, 2011: SMR major, ASMR IV[3] • ASMR maintained in re-evaluation of November 6, 2013[4]	June 7, 2017[5]	• SMR downgraded to insufficient (i.e., no longer reimbursed) in the case of treatment naïve patients regardless of B-RAF status, and 2nd line B-RAF+ patients • ASMR V continues to apply to 2nd line B-RAF- and 3rd line+ regardless of B-RAF status	• RWE in early line patients deemed obsolete because collected before launch of paradigm-changing I-O and other targeted agents • However, Yervoy monotherapy in advanced patients is seen as valuable

ASMR=Improvement of Medical Benefit (Amélioration du Service Médical Rendu)
ATU=Temporary Authorization for Use (Autorisation Temporaire d'Utilisation)
CEPS=Economic Committee of Health Products (Comité Economique des Produits de Santé)
CSEVR=Committee for Studies in Real Life (Comité des Études en Vie Réelle)
I-O=Immuno-Oncology
SMR=Medical Benefit (Service Medical Rendu)

- the observational, prospective, non-comparative IMAGE study conducted at the request of the European Medicines Agency (EMA)
- several retrospective cohort studies from the U.S.
- an electronic medical record study from a U.S. oncology network
- Cytokine Working Group data
- retrospective cohort study using compassionate use data from multiple countries

However, in the end, all of it was essentially discarded as no longer relevant due to market evolution.

Careful consideration of the potential impact of RWE on pricing and reimbursement (P&R) decisions, including reassessments in France, is required to guide investment decisions. It is becoming increasingly important to show products' effectiveness and safety in the real world – regardless of whether in post-launch or in early access such as with an ATU program - beyond efficacy and safety in an internally valid trial. As the case of the Myozyme registry shows, beginning with the end in mind is critical to mitigating P&R decision-makers' uncertainty. ■

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Pregnancy Registries and Lactation Studies
Best Practices to Support Product Labeling

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Fewer than 10% of drugs on the market have adequate data on safety of use in pregnancy and lactation,[1] yet over 90% of pregnant women use some type of medication while pregnant.[2] There are many reasons for the use of these drugs, including chronic conditions that require continuous treatment (e.g., asthma, epilepsy, diabetes); acute conditions that arise during pregnancy (e.g., infections, high blood pressure); and inadvertent drug exposure before the woman realizes she is pregnant. All patients, and especially pregnant patients, should have access to needed medications that have been adequately studied and be provided with information to enable them to assess the risks and benefits of using this medication. Thus, the need for studies focusing on the safety of medication use among pregnant and breastfeeding women is clear.

Regulatory Landscape

Since the thalidomide tragedy 50 years ago, the U.S. Food and Drug Administration (FDA) has required that medicinal products undergo testing to determine reproductive effects in animal models. However, animal models are not always reflective of the human experience. There is increasing interest in monitoring safety of drug use in human pregnancies. In 2002, the FDA issued guidance for industry in establishing pregnancy exposure registries.[3]

EMA followed with guidance on Exposure to Medicinal Products During Pregnancy in 2005.[4] With the passage of the Food and Drug Administration Amendments Act (FDAAA) in 2007, pregnant women were designated a special population and the FDA was granted the authority to mandate pregnancy registries. More recently, the FDA's Pregnancy and Lactation Labeling Rule (PLLR)[5,6] was issued which specifies the content and format of information presented in prescription drug labeling. The new Rule is intended to assist health care providers (HCPs) in assessing benefit versus risk and subsequent counseling of pregnant women and breastfeeding mothers regarding medication use. While the PLLR went into effect on June 20, 2015, it applies retroactively to all human prescription drug and biological products approved after June 2001 and requires companies to comply with these new regulations for all medications from that date (with a three-year grace period).

Overall, the new labeling requirements provide a much more robust description of product safety related to human reproductive issues *(Figure 1)*.

According to the FDA, there are currently 102 active pregnancy exposure registries,[7] which is a significant

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increase in the last three years.[8] Pregnancy registries have a fairly long history, with one of the first pregnancy registries having started over 30 years ago. Lactation studies on the other hand are still relatively rare. Due to the specific nature of these studies, there are clear and major differences compared to clinical trials and other observational studies and registries. Pregnancy and lactation studies have unique needs in terms of study design, recruitment and retention, data collection, and comparator data, and often require hybrid methodologies or innovative study designs to ensure a successful study.

Figure 1.
Examples of New Labeling Requirements under the PLLR[6]

- State if a pregnancy registry exists for that product, and if so, provide the contact information for the registry
- Include a risk summary of what is known about the potential risk of exposure during pregnancy, preferably based on human data. If there is no data to inform risk, include a statement to that effect
- Include a brief description of the data used to support statements made in the risk summary (if a pregnancy registry exists that has sufficient data to be able to make a statement about the risk of the product, the registry and data should be described)
- In the clinical considerations section, include information about the possible impact of untreated disease so that prescribers and their patients can make more informed decisions about the risk versus the benefit (e.g., for an asthma treatment, include a description of the effects of poorly controlled asthma on pregnancy)
- Include information on special dosing adjustments in pregnancy, if applicable
- Include a lactation section to provide information on the use of the product while breastfeeding, such as the amount of product in breast milk and the effects of the breast milk on the infant (data to include in this section typically comes from clinical lactation studies)
- Include a section on male reproductive risks

Pregnancy Registries

Prospective pregnancy registries are voluntary, observational, exposure-registration, and follow-up studies. Women are enrolled prospectively while still pregnant and before any knowledge of the pregnancy outcome through prenatal testing. This prospective orientation helps avoid bias that may be introduced by retrospective reporting. An active data collection system is used as opposed to a passive surveillance system and typically collects data from multiple reporters, including the pregnant woman herself, her HCPs, and the infant's pediatrician if a live infant is born.

Enrollment Process

To maximize enrollment, all eligible pregnant women exposed to the product of interest are allowed to participate. This remote enrollment process is facilitated by a central site and Principal Investigator (PI) to remotely oversee the registry and monitor participants and their infants for safety. Participants do not need to be located near a registry site and can enroll from anywhere in the country. For global pregnancy registries, there is a central PI in each country who then submits the country-specific regulatory and ethics committee documents and monitors women from their respective country. A registry contact or call center is established to assist the PI in all aspects of the pregnancy registry including awareness, enrollment, and data collection. Once a woman is made aware of a registry, she reaches out to the contact center where a representative provides a description of the registry and answers any questions she might have about enrollment or participation. If the woman is interested, the contact staff then assess her eligibility to participate in the registry. Once the woman is determined to be eligible, the contact staff facilitate the informed consent process, which includes medical release consent for HCPs to report data to the registry. The contact staff collect enrollment data from the participant over the phone and then they contact the applicable health care providers to collect clinical data.

How and from whom data are collected can affect the accuracy of the data. It is critical to collect the right data from the right reporter. Women typically know more about their habits and drug compliance than HCPs. Women can provide information on whether prescribed medication was actually taken, as well as habits and lifestyle factors that could impact the pregnancy. HCPs can provide more complete and accurate data on maternal, fetal, and neonatal diagnoses and clinical outcomes, especially clinical outcomes of interest (e.g., congenital malformations, preterm birth, small for gestation age, etc.). For example, the prescriber or treating physician can provide important data on the disease and disease severity. The obstetrician can provide data on the pregnancy and pregnancy outcome, and the pediatrician can provide data on the infant. These data are collected at various time points: 1) at enrollment or shortly after

enrollment; 2) midway through the pregnancy; and, 3) at pregnancy outcome. If a live infant is born, the pediatrician provides pediatric follow-up data. The FDA and other regulatory authorities generally require a twelve-month infant follow up, but this can vary. Some registries only collect information at pregnancy outcome, while others collect information as far out as three to five years of age for the child.

For optimum enrollment, it is critically important to keep things simple and allow multiple means for enrollment (e.g., phone, website, mobile devices). Depending on the country regulatory and privacy regulations, streamlining the consent process may also be possible. For example, in the U.S. and a few other countries, post-marketing requirements allow for a verbal consent process, which can greatly facilitate enrollment. Also, a simple data collection process will facilitate enrollment and retention. Thus, it is important to ensure the case report forms are as short and simple as possible. There is often a temptation to add more data fields than are truly needed, which can dissuade participation by both patients and health care providers.

> Patient recruitment is one of the greatest challenges faced by pregnancy registries.

Timing of enrollment is also critical. Enrolling patients as soon as possible after conception or after the exposure is extremely important for two reasons. First, it allows the capture of early pregnancy events. Second, enrolling pregnancies early before the outcome or the presumed outcome is known through prenatal testing is important to avoid selection into the registry based on presumed knowledge of the potential outcome. For example, some women may be relieved to know their baby does not have any problems after prenatal testing and are therefore more willing to enroll in the registry. Alternatively, some women may enroll because their baby does have a birth defect identified on a prenatal test. Either scenario can introduce bias either towards a lower or higher risk of birth defects. Understanding which types of prenatal tests can assess birth defects is also important. The first trimester dating ultrasounds do not assess fetal malformations, but tests, such as the nuchal translucency, chorionic villus sampling, amniocentesis, alpha fetal protein measurements, and second trimester ultrasound do assess for malformations. Thus, enrolling patients before these tests are performed is important.

Recruitment

Patient recruitment is one of the greatest challenges faced by pregnancy registries. Because registries typically use the patient-centered approach rather than a traditional site-based approach, it is important that the registry casts a broad net in their awareness efforts including outreach to both health care providers and pregnant women. A robust awareness plan should be designed specifically for each registry accounting for the particular product, target population, geographic scope, and most importantly, the goals of the registry. The internet and social media are important recruitment sources for pregnant women and personal mailings, medical science liaisons (MSLs), and scientific venues are important recruitment initiatives for health care providers. Awareness plans typically include a mixture, if not all, of the avenues outlined below.

- **The FDA requirement** that the registry and contact information be mentioned in the product label is very helpful in ensuring providers and patients are made aware of each registry.
- **Outreach to clinicians** (not only physicians, but nurses, nurse practitioners, midwives, etc.) is crucial to the recruitment effort. The vast majority of women are referred to pregnancy registries through their health care providers, and since women often spend time with nurses as well as doctors, it is important to include all types of clinicians.
- **A registry brochure** is typically created to provide information on the registry, why it is being conducted, and the procedures involved in participating. This brochure, an introductory letter, and sample data collection forms are then sent to all applicable health care providers to educate them on each registry.
- **Medical science liaisons** outreach - they visit prescribers on a regular basis and can provide more in-depth information about the registries.
- **Attendance at scientific and professional conferences,** including exhibit booths where knowledgeable staff can distribute the brochure and answer questions and conference presentations on the registry methods (or data if available).
- **A registry website** should be established where women and HCPs can find information on the specific registry, including contact information.
- **Social media** is growing in popularity as a means of awareness as well, especially with younger women spending so much time on social media outlets. LinkedIn, Twitter, and Facebook are all examples of social media outreach channels.
- **Advocacy groups** can also be a great source of awareness, especially for certain diseases where active advocacy groups exist. Often advocacy groups will provide a link to the pregnancy registry website from their website, informational articles or ads about the pregnancy registry in group newsletters, etc.

There is limited hard evidence on the effectiveness of awareness activities for pregnancy registries, however, systematic examination of enrollment patterns in

pregnancy registries following various awareness initiatives have indicated that multiple, persistent awareness activities have the greatest impact on enrollment, especially activities tapping into the internet and social media.[9]

Comparator Data

Given the inherent difficulties in identifying an appropriate comparison group, multiple methods may be used to review the data for signals. There are two basic types of comparators used to put potential signals into context in pregnancy registries including internal comparators and external comparators.

Internal comparators include pregnant women who are enrolled concurrently into the registry who do not have the exposure of interest. These women may: 1) have the disease of interest but they have not been exposed to the registry product; 2) be healthy volunteers; or, 3) be a combination of both. Many registries use both a disease comparator and a healthy volunteer comparator. The advantage of using internal comparators is that they undergo the same processes as the exposed group, including definitions and assessments of outcomes and covariates that could impact outcomes. Additionally, adjustments for differences in characteristics and covariates can be done in the analysis. While internal comparators are generally thought to be scientifically superior to external comparators, it is important to remember these studies are still observational and not carefully controlled clinical trials. Thus, the comparator group, even if enrolled internally, could still vary on important characteristics from the exposed group. Other limitations include difficulty in enrolling an internal comparator, as there is little incentive for unexposed women to participate in a pregnancy registry. Finally, enrolling an internal comparator has an impact on study size and costs since two to three times as many participants are needed.

External comparators can include other prospective registries or studies; secondary data sources, such as electronic medical records (EMR) or claims databases; published data; national vital statistics; or population-based comparators, such as the CDC's Metropolitan Atlanta Congenital Defects Program (MACDP)[10] or the European Surveillance of Congenital Anomalies (EUROCAT).[11] This approach requires a detailed evaluation of background rates from external surveillance sources and published literature to identify comparable rates of pregnancy outcomes and congenital anomalies. Background rates in the general population on infant mortality and other pregnancy outcomes, such as premature birth, are readily available from national vital statistics or publications in the scientific literature. Published rates of birth defects are available from the CDC's MACDP or EUROCAT. These population-based comparators are commonly used because they typically have large sample sizes and can provide stable risk estimates for specific birth defects.

However, rates in the general population are not an ideal comparator because the methods of ascertainment differ from those of a pregnancy registry and the population may differ greatly on important characteristics or factors that could impact pregnancy outcome. When relying on external comparators it is critical to identify differences between the registry population and comparator group and to thoroughly understand the methodology and factor these differences into the analysis plan.

When studying a population with a disease that impacts the pregnancy outcome, such as asthma, multiple sclerosis (MS), or diabetes, it is important to identify a comparator with the underlying disease rather than using a population-based comparator. The comparator should be appropriate to the population under study, and when possible, use the same methodology and definitions as the registry. However, this may not always be possible. What is important to remember is that there is no ideal comparator for a pregnancy registry. Using multiple comparators may improve the validity of your findings.

Summary

Over the last 30 years, pregnancy registries have been used to systematically collect much needed data on safety of medication use in pregnancy. Well-designed pregnancy registries offer a unique opportunity to collect information on pregnancy exposures early in a product's life cycle, when interest in the product and safety is highest. Pregnancy registry data have been used to support label changes[3] and will continue to provide much needed human data to support the new Pregnancy and Lactation Labeling Rule.

Lactation Studies

Lactation studies are relatively new and much less common than pregnancy registries, Thus, there is still much to be learned. Study approaches are evolving and there are numerous barriers to overcome in developing the ideal study design. Some lactation studies have been conducted in Phase I units where the mother is required to spend a 24-hour period in the unit providing breast milk samples. Other studies require that mothers collect breast milk samples at home and deliver them to a study site on a periodic basis. These study designs are onerous for new mothers who rarely have the time or inclination to make this commitment to a study when their priority is spending time with their newborn. There is also the challenge of finding pregnant women during the narrow window of pregnancy or shortly thereafter, who have the exposure of interest and who intend to breastfeed. Additionally, while pregnancy registries are observational in nature (participants are observed and data on outcomes are collected), lactation studies are considered interventional because they require the collection of biological samples. Because they are considered interventional, lactation studies often have more rigorous regulatory and ethics

requirements than observational pregnancy registries. One advantage of lactation studies is that they require fewer subjects, typically fewer than 20, while pregnancy registries usually require 250 to 500 participants.

Since lactation studies have numerous barriers and challenges, it is important to try different approaches to designing these studies. Below is a case study of an innovative approach that has proved successful in conducting lactation studies.

Conclusion

Prospective pregnancy registries and lactation studies, if conducted properly, can be very effective tools to support the new FDA labeling rule, as well as provide much needed human data to help health care providers and prospective parents in making informed treatment decisions during pregnancy and lactation. ■

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Case Study

Background

A post-authorization safety surveillance study was conducted in several countries in North America and Europe. The objective of the study was to determine whether the product of interest was transferred to breast milk. The ultimate goal of the study was to generate robust data to include in the product label so that women treated with the product considering breastfeeding and their treating physician could make informed decisions for the benefit of mother and child.

Approach

A traditional site-based approach was combined with a remote enrollment model whereby women were allowed to self-enroll through a central site. This hybrid approach sought to enroll all eligible women, even those that were not located near a traditional study site. Investigators had the option to enroll subjects treated at their site (i.e., traditional model) or monitor subjects who self-enrolled remotely via phone.

Traditional sites would identify appropriate patients from their practices and enroll them in a standard site-based study approach. The remote enrollment approach permitted all eligible women to enroll through a central PI. In this model, women would call the Remote Coordinating Center (RCC), the remote study coordinator would screen the woman for eligibility over the phone, and obtain her consent to a physical assessment. The woman would then undergo the physical assessment by her local health care provider, who then completed the necessary

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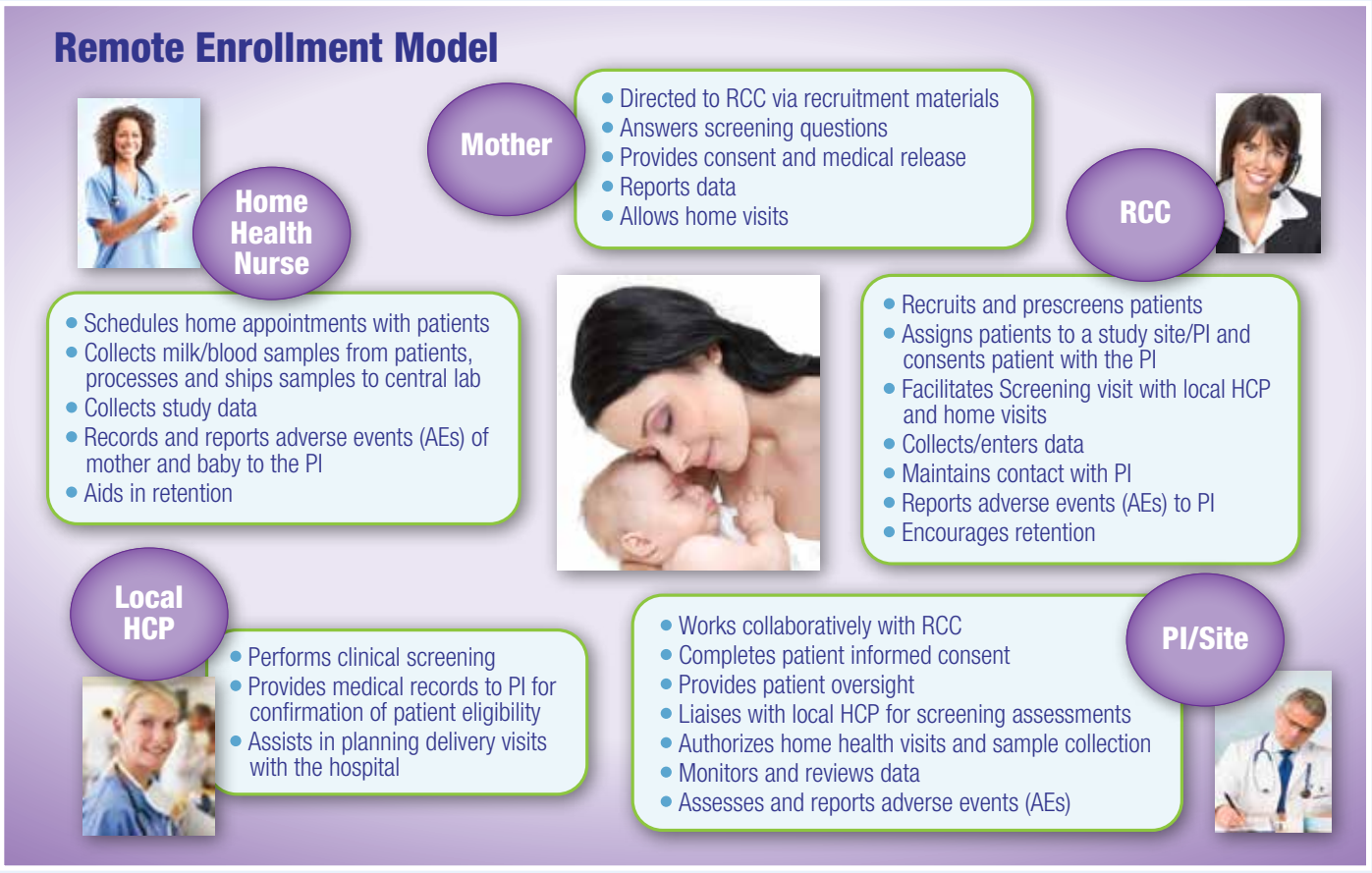

Case Study - CONTINUED

paperwork and sent it into the RCC. Since these studies are interventional, informed consent was required and those discussions occurred over the phone and then forms were sent by courier, signed, and returned to the RCC. The remote enrollment process allowed all eligible women to participate without traveling to a specific study site.

Study subjects enrolled through either process were visited by home health nurses who collected the breast milk samples and other relevant information, as well as any adverse events experience by the mothers or their babies. The study required that breast milk samples be collected nine times within 28 days starting at six weeks post-partem. All samples were then sent to the central lab for processing. This simplified the process for the new mothers, removing significant time and travel barriers.

Results

This hybrid model proved to be very successful and was generally accepted by the regulatory agencies and ethics committees in all the participating countries. However, not all the investigators accepted the remote enrollment option. For example, many investigators in the European countries chose the traditional site model or used a modified version where a single investigator served as the national coordinator for multiple sites within that country. In North America, the hybrid model boosted enrollment by 75% which never would have been accomplished using only traditional site enrollment. While the remote enrollment model was not accepted by most European investigators, enrollment flourished using the traditional sites.

The collection of samples and information by the home health nurses resulted in 100% of the visits being completed, 99% were completed within the specified timeframe, and 100% of the data collection forms were accurate and complete.

Impact

While lactation studies present unique challenges, using a hybrid approach provided access to a subject population that may not otherwise have been willing or able to participate. The home health approach helped reduce the burden on the new mothers making them more willing to participate and ensuring timely and accurate collection of the samples and data. By conducting these studies, robust data can be provided to better inform treatment decisions for women with chronic diseases considering breastfeeding. Within one year of study completion, the product label was updated with data from the study and submitted and approved by regulatory authorities.

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Using Qualified PRO Measures in Drug Development
An Update on the EXACT and E-RS

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Introduction

Testing treatment effects in clinical trials requires outcome measures that are reliable, valid, and sensitive to change. To facilitate the use of appropriate and precise patient-reported outcome (PRO) measures in pharmaceutical trials, regulatory agencies in the United States (U.S.) and Europe have published guidelines covering specific therapeutic areas,[1-3] describing the use of PRO measures[4,5], and outlining procedures for qualifying drug development tools (DDTs).[6,7] The EXAcerbations of Chronic pulmonary disease Tool (EXACT®) and Evaluating Respiratory Symptoms scale (E-RS™) were the first tools to undergo the qualification review process and be qualified by both the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA). This paper describes the EXACT and E-RS and some of the insights gained through their use post-qualification.

The Exacerbations of Chronic Pulmonary Disease Tool (EXACT)

Many patients with chronic obstructive pulmonary disease (COPD) experience acute deteriorations of their condition, known as exacerbations, that are not only disconcerting to these individuals but can have significant short- and long-term health consequences. Understanding the risk factors and characteristic features of exacerbations are important areas of study, and reducing their frequency and severity are key treatment objectives of pharmaceutical sponsors and clinicians. The EXACT was developed to meet the need for a direct measure of patient-reported symptoms of exacerbation in clinical trials testing the effects of pharmaceutical agents on exacerbation frequency, severity, and duration.[8-11] This 14-item daily diary complements and extends information provided by traditional health care resource utilization (HCRU) data by standardizing the evaluation of symptoms around medically treated events. Using the unidimensional interval-level scale score produced by the EXACT, the symptom severity associated with events treated in the clinic or emergency room can be quantified in absolute terms (0 to 100, higher scores are worse) or the magnitude of change from baseline or stable state. Daily scores can also be used to evaluate changes leading up to and following events, including hospitalization.


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In addition to quantifying HCRU-associated events, the EXACT captures acute sustained worsenings of COPD that are not seen or treated by clinicians, yet adversely affect patient lives.[8,12-14] Because these events are not seen by a clinician, they are identified through a daily diary; in the case of the EXACT they are identified using a validated scoring threshold indicating an acute sustained worsening has occurred (9 points for 3 days, 12 points for 2 days). This yields data on frequency, severity, and duration of these symptom-defined events, again complementing and extending the information provided by HCRU-defined exacerbations.

The EXACT was developed to quantify exacerbation outcomes in trials testing the efficacy of therapies to treat acute exacerbations of COPD or prevent them from occurring, using retrospective data analyses for hypothesis testing. The measure was not designed for prospective use, such as signaling an upcoming exacerbation or prompting patients to call their clinician and seek care. The latter is not recommended in pharmaceutical trials because it could change patient diary response behavior and alter trial results. Licensed users of the EXACT choosing to try these alternate applications of the instrument are encouraged to test them and disclose that these are new uses of the instrument.

Qualification: On 9 January 2014, the FDA released their Draft Guidance for the EXACT[15] and on 13 April 2015, the EMA released their Draft Qualification Opinion for the EXACT and E-RS.[16]

The Evaluating Respiratory Symptoms (E-RS) in COPD Measure

The E-RS is a derivative instrument using the 11 respiratory symptom questions from the EXACT to quantify respiratory symptom severity in stable COPD.[17,18] During development, confirmatory factor analysis supported a second-order model with a general factor, representing respiratory symptom severity overall (E-RS Total), and three domains or subscales representing the three key respiratory symptoms of COPD: RS-Breathlessness, RS-Cough and Sputum, and RS-Chest Symptoms. E-RS 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. A step-down approach can be used, with the E-RS Total tested first, followed by the three subscales.

During the qualification process, the submitted name of this instrument was the EXAcerbations of Chronic Pulmonary Disease Tool-Respiratory Symptoms (E-RS), referencing its parent instrument. During the development of the qualification statement for this measure, the FDA requested a name change so the term "Exacerbation" would not appear in labeling related to symptoms of stable disease. To address this request, the name was changed to the "Evaluating Respiratory Symptoms" measure

The EXACT was developed to quantify exacerbation outcomes in trials testing the efficacy of therapies to treat acute exacerbations of COPD or prevent them from occurring …

(retaining the E-RS acronym while avoiding the term exacerbation), adding "COPD" (E-RS:COPD) to specify the target population. All presentations and publications post 2016 (should) refer to this instrument as the Evaluating Respiratory Symptoms tool.

In any given study, the 14-item diary can be used either to evaluate exacerbations of COPD (EXACT scoring algorithm), respiratory symptoms in stable COPD (the 11-item E-RS:COPD scoring algorithm) or both.

Qualification: As noted above, the EMA released their Draft Qualification Opinion for the EXACT and E-RS on 13 April 2015[16] and on 8 March 2016 the FDA released their Draft Guidance for the E-RS.[19]

Use of the EXACT and E-RS:COPD Post-Qualification

The EXACT and E-RS have been widely used in clinical trials to measure treatment effects (40+ trials in clinicaltrials.gov), as well as in natural history and academic research (65+ academic licenses/studies), with more than 25 publications to date.[20] To protect the integrity of the instrument, Evidera licenses both measures and oversees and licenses all translations (now over 55). Licensing fees paid by for-profit organizations go to a research and development fund for these instruments and to facilitate licensing and free use by academic and not-for-profit investigators. The information below provides a high-level summary of some of the insight gained through research to date.

The EXACT

The EXACT has shown evidence of sensitivity to the effects of treatment on frequency of symptom-defined events, with patterns similar to those observed with HCRU frequency. For example, in the ATTAIN study, a 24-week international Phase III randomized, controlled clinical trial testing the efficacy of aclidinium for the maintenance treatment of COPD (N=828), a significant difference in exacerbation rates between each active treatment group and placebo for both HCRU and symptom (EXACT)-defined events was observed.[21] In a non-pharmaceutical setting, Halpin and colleagues' 4-month randomized trial of the effect of health risk winter alert calls on exacerbation rate found that patients receiving calls had fewer symptom (EXACT)-defined events and that these events were shorter and less severe (area under the curve) than events seen in patients receiving no calls.[22] Although not statistically significant

due to sample size limitations, the large effect sizes were consistent with the EXACT's sensitivity to treatment effects, with results providing insight into the effect of weather and early intervention on exacerbations of COPD with implications for further research.

The EXACT has also been used to better characterize symptom-defined events, their impact on patient outcomes, and patient treatment-seeking behavior phenotypes. Secondary analyses of the ATTAIN data showed patients experiencing unreported symptom-defined exacerbations had longer symptom-defined exacerbation recovery times, greater deterioration in lung function, and worse health status scores at the end of the study.[21]

Mackay and colleagues[23] showed that among symptom-defined exacerbations captured with the EXACT, patients with more severe stable disease (defined by history of exacerbations in the last year and airflow obstruction) were more likely to report events and receive treatment for symptom-defined exacerbations associated with smaller increases in symptom severity at event onset compared to patients with milder stable disease.[23] A secondary analysis of pooled data from two 12-week Phase II international randomized controlled trials using the EXACT to identify symptom-defined exacerbations found that patients who failed to recover from symptom-defined exacerbations (persistent worsening) had significantly lower EXACT scores at baseline and more gradual event onset compared with patients who recovered.[24] These findings suggest that patients with lower EXACT scores at baseline, and patients with more gradual symptom deterioration, may be less likely to report acute symptomatic events. Symptom-defined exacerbations with a more gradual onset may be more difficult for patients to identify as an acute worsening in their COPD health that is worth a health care visit for assessment and possible treatment. Results also suggest difficulty recovering from symptom-defined exacerbations leads to a decline in health status and increased levels of breathlessness and chest symptoms that may represent an early signal of disease progression.

There has been significant interest in incorporating digital instruments and wearable technologies as complementary endpoints in clinical trials. In a small, non-interventional study of 17 patients, Ehsan and colleagues[25] found a significant decrease in physical activity, measured through an activity monitor, during symptom (EXACT)-defined events that persisted for two weeks following symptomatic recovery. These events were also characterized by increased daytime sleepiness, decreased total sleep time, and decreased sleep efficiency (measured via actigraphy).[26]

Among the Challenges

A major challenge with the use and interpretation of the EXACT has been a misunderstanding of the relationship between symptom-defined and HCRU events. Data from

> The FDA's qualification program for clinical outcome assessments and biomarkers facilitates discussion between instrument developers/advocacy teams and regulatory agencies to make certain interests are aligned.

clinical trials and observational studies have consistently shown a low concordance or "agreement" between these two types of events.[10,21,23] This is interesting and important information to help us better understand exacerbations, particularly those treated in the clinic, emergency room, or hospital. The low concordance is not a validity coefficient for either the EXACT or HCRU metric, but rather a function of threshold variability - the quantitative threshold required to identify unreported symptom-defined events, patients' qualitative threshold for seeking care, and clinician thresholds for diagnosis and treatment. Symptom-defined events are a sustained worsening in the patients underlying condition that are identified using a standardized, quantified score that exceeds normal day-to-day score variability. In contrast, HCRU events are clinic visits, driven by the patient's decision to seek care and diagnosed and treated by the clinician based on his/her judgement and practice setting. The HCRU event is observed and counted, however the patient and clinician behaviors related to that observed event are not standardized or quantified. Some patients are "less symptom tolerant" and seek care early, while others are more "tolerant" (or have other things to do) and decide not to seek care. Clinicians have different standards of diagnosis and treatment; health care systems have different standards for hospitalization (that could lead one to erroneously conclude that patients in some countries have more severe exacerbations when, in fact, this is due to admission policy). Symptom severity associated with HCRU events are highly variable, with milder HCRU events failing to meet the threshold for a symptom-defined event.[10,21] This simply indicates that some HCRU events are symptomatically mild, and that unreported events can be even more severe than those seen and treated. The EXACT offers data to better understand HCRU events, including the relationship between patient symptoms (magnitude, change, type), preferences, care-seeking behaviors, clinical assessment, and treatment, as well as insight into the day-to-day variability of symptoms outside the clinic setting.

The E-RS:COPD

The E-RS:COPD has been used successfully in a number of trials testing the effect of treatment on respiratory symptoms of COPD. In the ATTAIN study, statistically significant and clinically meaningful treatment effects were observed for the RS-Total score and each of the subscale scores.[27] Results of pooled data from the ATTAIN and AUGMENT Phase III trials comparing aclidinium bromide

and placebo also showed significant treatment effects for the RS-Total and subscale scores overall and by GOLD status.[27] Importantly, these results are referenced in the EMA Summary of Product Characteristics (SPC) for Duaklir Genuair, indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. "Duaklir Genuair improved daily symptoms of COPD such as 'breathlessness', 'chest symptoms', 'cough and sputum' (assessed by E-RS:COPD total score) (EMA Summary of product characteristics, pp. 10[28])." This was the first appearance of the E-RS:COPD in a label.

E-RS:COPD effects were also observed in a 6-week Phase IIIb randomized, controlled, multicenter clinical trial conducted in the Czech Republic, Germany, Hungary, and Poland, testing the efficacy of aclidinium versus placebo and tiotropium on COPD symptoms (N=400). This study showed a significant effect of aclidinium bromide and tiotropium on respiratory symptoms versus placebo.[29]

A secondary analysis of pooled data from two Phase III, 24-week randomized, placebo-controlled trials of twice-daily aclidinium/formoterol (the ACLIFORM and AUGMENT studies), the efficacy of treatment compared to placebo or monotherapies in patients defined as less/more symptomatic using an RS-Total score ≥10/<10, respectively was conducted.[30] In more symptomatic patients, aclidinium/formoterol improved RS-Total score from baseline vs. placebo or both monotherapies.

The E-RS was used to evaluate respiratory symptom severity in the FULFIL study, a Phase III, 24-week randomized, double-blind, double-dummy, multicenter study comparing once-daily single inhaler triple therapy [fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI)] with twice-daily inhaled corticosteroid/long-acting β2-agonist therapy [budesonide/formoterol (BUD/FOR)] in patients with symptomatic COPD at risk of exacerbations.[31]

FF/UMEC/VI showed greater reductions from baseline in RS-Total and all subscale scores compared with BUD/FOR, with treatment differences statistically significant for each 4-week interval. The FF/UMEC/VI group exceeded the RS-Total responder threshold at 8 weeks compared to BUD/FOR and the RS-Breathlessness and RS-Cough and Sputum score changes which exceeded their responder thresholds by week 12.

New Uses for the E-RS – the E-RS:IPF

Thanks to the experiential knowledge and insight of 84 people with COPD during instrument development and content validation, and input from clinical and measurement experts, the E-RS covers the key respiratory symptoms experienced by people with COPD, with questions and response options easy for patients to read and rate. These symptoms (breathlessness, cough, sputum, and chest congestion) are not unique to COPD. The content, intuitive simplicity, and ease of patient use make the E-RS appealing as a PRO measure for other conditions affecting the respiratory system. An instrument cannot be transported from one target population to another without testing, however. Assurance is needed that the instrument is content valid and yields scores that are reliable, valid, responsive, and interpretable in the new target population.

There is qualitative and quantitative evidence to suggest the E-RS may be useful for trials of idiopathic pulmonary fibrosis (IPF).[32] As one might expect, the individual items comprising the E-RS map nicely to the IPF respiratory symptoms, however the structure of the measure and scoring are different. Unlike the E-RS:COPD, there is no total score. Rather, the E-RS:IPF has four scale scores corresponding to the key respiratory symptoms of IPF: breathlessness, cough, sputum, and chest symptoms, with any or all potential endpoints in clinical trials.[32]

A Perspective on EXACT and E-RS Qualification as Exploratory Endpoints

The FDA's qualification program for clinical outcome assessments and biomarkers facilitates discussion between instrument developers/advocacy teams and regulatory agencies to make certain interests are aligned. As the first PRO measures to be reviewed and approved under this evolving process, the EXACT and E-RS were both qualified as exploratory endpoints. Although initially disappointing, it became clear that the exploratory designation serves an interesting role for regulatory agencies and sponsors. By qualifying these instrument, the agencies acknowledged familiarity with the measures and agreed with the supporting evidence to date, including its content validity, reliability, quantitative validity, responsiveness and interpretation guidelines within the context of use described in the submission documents and outlined in the qualification. As the instruments are used by industry and academic scientists, evidence and understanding will continue to grow. Sponsors can talk with regulatory agencies about the use of the instrument(s) in their program(s) with this foundation. No need for sponsors to describe the measure(s) in detail or submit an instrument dossier. Discussions can proceed directly to the suitability and positioning of the measure(s) for their program based on the product profile, target population, stage of development, other proposed endpoints, and endpoint positioning. If the instruments are included in proof-of-concept or Phase II trials, these meetings can include a discussion of measurement properties and efficacy signals in their specific drug, target population, and trial designs to further inform conversations related to Phase III endpoint hierarchy and labeling claims. Agency decisions on the use and positioning of instruments qualified as exploratory endpoints, like the EXACT or E-RS, can be made on a case-by-case basis, informed by the unique elements of each case. Seen in this light, qualified measures like the EXACT and E-RS should be considered part of the drug development "tool box", ready for use in drug development programs as interests and needs arise.

Conclusions

When we started the EXACT journey a dozen years ago, it was clear the field needed a standardized method to quantify exacerbations of COPD to understand these important yet elusive events and their impact on health and quality of life. The journey has been filled with "firsts" and insight that accompanies exploration – first PRO consortium (thank you to all who participated; it was a pleasure!); first through the qualification process (submission pre-dated the guidance - thank you FDA colleagues for your interest, enthusiasm, and persistence!); first parallel PRO submission to the EMA (thank you EMA colleagues for your time, interest, and insight!); and, first qualified by both agencies (exploratory is a first step!).

Work on the EXACT led to the development of new symptom measures for studies of COPD and IPF. Our understanding of COPD exacerbations, symptom burden, and the effects of treatment on these patient experiences is growing as the measures are used in descriptive, natural history and interventional studies and results are shared through presentations and publications. Scientists and clinicians are asking new questions, approaching research in new ways, digging into data to uncover patterns and insight. May the journey continue. ■

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> Somewhere, something incredible is waiting to be known." – *Carl Sagan*

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> "It is not the strongest of the species that survive, nor the most intelligent, but the one most responsive to change." – *Charles Darwin*

Observational (NIS) Studies in Conjunction with Utilization of Patient Support Programs

Ekaterina Z. Borcheva-Dancheva, MD
Associate Director Regulatory Affairs, PPD

Krista A. Payne, MEd
Vice President and General Manager, Real-World Evidence, Evidera

One very important outcome of the International Council for Harmonization (ICH) meeting held in Osaka, Japan, November 5-10, 2016, was the amendment of ICH E6(R2)[1] (issued February 2017). The intent of this amendment was to encourage sponsors to implement improved oversight and management of clinical trials, and protect clinical trial data integrity while continuing to ensure the protection of human clinical trial subjects. The Assembly agreed to renew the wider package of guidelines that relate to good clinical practice (GCP) and clinical trial design, which includes updating the current guidance on interventional trials and the expansion of novel methods in support of drug registration, such as non-interventional studies (NIS), including registries and other observational study types.

The European Medicines Agency (EMA) guidance[2] increasingly requires the collection of risk-benefit data in post-authorization safety studies. Pharmaceutical companies now must take a more granular approach, examining different subpopulations to determine their respective risk-benefit balance. There is also an increasing demand from payers to conduct observational studies on a new product's effectiveness, and payers and clinicians are eager for more detailed health outcomes data to inform prescribing and reimbursement decisions.[3]

Innovative real-world study designs are also warranted in support of successful market access and reimbursement, particularly in crowded markets.

Patient Support Programs and Real-World Data Collection

Good pharmacovigilance practices (GVP) Module VI[4] defines the patient support program (PSP) as an organized system where a marketing authorization holder receives and collects information relating to the use of its medicinal products. Examples are post-authorization patient support and disease management programs, surveys of patients


Ekaterina Z. Borcheva-Dancheva


Krista A. Payne

and health care providers, and information gathered on patient compliance or compensation/reimbursement schemes. Given the importance of patient wellness and the health benefits of compliance to effective treatments, PSPs are increasingly common. Through PSP frameworks, physicians receive additional information from patients and other qualified health care providers about adherence and health outcomes that can positively impact the patient through additional patient health monitoring, resulting in improved treatment compliance. Patients benefit through access to comprehensive information about their disease, disease control, and correct drug use and handling. PSPs also typically facilitate increased connectivity among patients and improved communication between patients and their physicians.

Patient support programs[5] are a useful addition to:

1) complex therapies with many side effects;

2) therapies requiring a series of treatments and/or ongoing monitoring/regulating;

3) therapies for diseases that negatively impact quality of life; and,

4) therapies requiring a delivery device.

Patient support programs drive medication and therapy compliance via:

- Inbound call support for inquiries on products, diseases, or program enrollment
- Helping patients make or break a habit
- Outbound calls to patients to support/coach them through their treatment with relevant messages and information
- Referrals to other information sources inside and outside the biopharmaceutical company
- Safety measures that mitigate risk with proper identification and reporting of adverse events to Drug Safety Structures
- Comfort and support that builds engagement

Given the enormity and cost of PSPs, real-world studies of PSP effectiveness to demonstrate their value are also occurring more frequently.[6] Randomized trials have demonstrated the effectiveness of tailored education and support compared with a "one size fits all" approach to help patients modify a range of health-related behaviors.[7] As well, numerous non-comparative, real-world studies of outcomes associated with PSPs plus treatment have also been published.[8]

Case Study: Observational Study of Treatment Outcomes in a Patient Support Program[9]

Study design: Non-interventional, longitudinal, and non-confirmatory study to explore rheumatoid arthritis (RA) treatment effectiveness and patient satisfaction.

The main objectives of the study were to:

1) examine the effectiveness of RA treatment with respect to PSPs by means of the Health Assessment Questionnaire Disability Index (HAQ-DI), Disease Activity Score (DAS28) results, and European League Against Rheumatism (EULAR) response criteria; and,

2) evaluate the contribution of PSP to disease control, treatment continuation over time, participant's satisfaction, and PSP utilization.

The primary endpoint was to determine the percentage of participants (18-99 years of age) achieving a minimal clinically important difference (MCID) in HAQ-DI at week 78.

Additional secondary endpoints included changes in:

- Disease Activity Score (DAS28) results
- Simplified Disease Activity Index (SDAI)
- Clinical Disease Activity Index (CDAI)
- Disease response criteria

Other assessments included:

- Work Productivity and Activity Impairment (WPAI)
- Compliance Questionnaire
- Treatment Satisfaction Questionnaire for Medication (TSQM) scores (effectiveness, adverse reactions, convenience, and global satisfaction)

The participant satisfaction over time in context with utilization of a patient support program (PSP) was measured by:

- Patient Activation Measure (PAM-13) – assessment of the participant's knowledge, skill, and confidence for self-management of his/her health
- Beliefs about Medicines Questionnaire (BMQ) – beliefs about medication and the necessity of medications prescribed with sub-scales of necessity and concerns. Higher scores on the necessity sub-scale represent the stronger perceptions of the participant for the necessity of their medication. Similarly, higher scores on the concerns sub-scale represent stronger concerns about the potential negative effects of their medications.
- PSP satisfaction assessment – evaluation of the participant's satisfaction with specific PSP elements

Patient Support Program core elements consisted of:

- Call centers (in and outbound)/hotlines
- Nursing services
- Starter packs
- Provision of educational materials (print and digital) regarding disease and treatment
- Treatment guides
- Other elements of the PSP varied between countries such as refill reminders, email contacts, support groups, and newsletters

Finally, serious adverse events (SAEs), adverse events (AEs) that resulted in treatment discontinuation, and non-serious malignant events were collected for patients 30 years of age or younger.

A total of 1,025 patients were enrolled in the study and received at least one dose of the RA treatment, with 679 patients completing the study. The study results (all with p-value <0.001) regarding the primary endpoint are represented below in Table 1.

Table 1. Percent of Participants Achieving MCID among PSP and Non-PSP Users

Participants with RA Receiving RA Treatment		
	PSP Users	**PSP Non-Users**
Participants Analyzed	499	526
Participants Achieving an MCID* in the HAQ-DI at Week 78	48.1%**	37.8%**

* Defined as at least a 0.22-point improvement on the HAQ-DI compared to baseline.
** **P-value** <0.001

The percentage of participants who demonstrated improvement from baseline or who remained at Level 4 [Levels: strongly disagree (1), disagree (2), agree (3), or strongly agree (4)] from baseline on the Patient Activation Measure (PAM-13) at Week 78 is presented in Table 2.

Table 2. Percent of Participants with Improved PAM-13 Scores among PSP and Non-PSP Users

Participants with RA Receiving RA Treatment		
	PSP Users	**PSP Non-Users**
Participants Analyzed	499	526
Participants Who Demonstrated Improvement or Remained at Level 4 from Baseline at Week 78 on the PAM-13	35.7%*	28.1%*
Participants Who Started and Remained at Level 4 from Baseline to Week 78 on the PAM-13	52.4% (54 out of 103)	28.9% (24 out of 83)

***P-value**=0.01

The changes from baseline means in the Beliefs About Medicines Questionnaire (BMQ) are presented in Table 3.

Table 3. Changes in Baseline Means on the BMQ among PSP and Non-PSP Users

Participants with RA Receiving RA Treatment		
	PSP Users	PSP Non-Users
Participants Analyzed	409	362
Change from Baseline Means at Week 78 on the BMQ		
Necessity		
Participants Analyzed	409	362
Mean (SD)	-0.03 (0.743)	-0.04 (0.729)
Concern		
Participants Analyzed	409	361
Mean (SD)	-0.12 (0.902)	-0.17 (0.842)

SD=Standard Deviation

PSP Satisfaction Questionnaire Responses at Week 78 are presented in Table 4.

Table 4. PSP Satisfaction by Score

PSP in Total: Score 1	Participants with RA Receiving RA Treatment: PSP Users
Participants Analyzed	336
PSP in Total: Score 1	34.2%
PSP in Total: Score 2	
Participants Analyzed	336
PSP in Total: Score 2	35.7%
PSP in Total: Score 3	
Participants Analyzed	336
PSP in Total: Score 3	1.5%
PSP in Total: Score 4	
Participants Analyzed	336
PSP in Total: Score 4	28.6%

1=Very Good; **2**=Good; **3**=Less Satisfying; **4**=I Do Not Use the Services

Baseline characteristics were similar between cohorts. During the follow-up period, the percentage of participants achieving a minimal clinically important difference in the (HAQ-DI) at week 78 was 10.3% greater in the PSP cohort than for the non-PSP cohort. The percentage of participants who either improved or started and remained at Level 4 from baseline to week 78 on the PAM-13 was 7.6% greater in the PSP cohort than for the non-PSP cohort. Patients in the PSP cohort demonstrated better understanding of medicine necessity and safety concerns. Patient satisfaction of PSP at week 78 was 98.5% in the PSP cohort.

Univariate analyses from similar studies demonstrated that medical costs for 12 months (excluding costs for biologic treatment) were 23% lower for PSP patients than for non-PSP patients. PSP patients were also found to have 22% lower disease-related medical costs than non-PSP patients. Finally, overall costs for PSP patients were 10% lower than those for non-PSP patients.[6]

PSPs contribute significantly to successful product uptake through improved patient compliance and outcomes. Given the infrastructure set-up, including call centers, nurse outreach, and multi-modal communication, they also provide an efficient framework for the collection of real-world data that can inform a variety of research questions of importance to patients, physicians, and payers alike.

Real-world studies of PSP effectiveness offer an opportunity to optimize access to innovative medicines and improve patient outcomes. Enrollment in the PSP is associated with increased treatment adherence and persistence, reduced medical costs (all-cause and disease-related), and reduced total health care costs. These data provide support for prescribing physicians to encourage enrollment in PSPs for chronic conditions and for pharmaceutical companies to further develop and invest in multifaceted PSPs.

For more information, please contact Ekaterina.Borcheva-Dancheva@ppdi.com or Krista.Payne@evidera.com.

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Evidera Presents at ISPOR 2018

May 19-23, 2018 – Baltimore, MD, USA

SHORT COURSE

Sun., May 20, 8:00 AM - 12:00 PM

Using DICE Simulation for Health Economic Analyses

Instructors: Caro JJ, Moller J

WORKSHOPS

Mon., May 21, 3:45 PM - 4:45 PM

W5: Adjusting for Between-Trial Differences in the Schedule of Assessment for Disease Progression in Immuno-Oncology and its Impact on Indirect Treatment Comparisons

Kapetanakis V, Schlichting M, Stevens JW

Tues., May 22, 11:00 AM - 12:00 PM

W9: Numbers or Noise? Interpreting Internal Validity Tests of Stated-Preference Data

O'Callaghan K, Johnson FR, **Marsh K**, Yang JC

Wed., May 23, 1:45 PM - 2:45 PM

W21: Principles of Effective Machine Learning Applications in Real World Evidence

Cox A, Ramagopalan S, Capkun-Niggle G, Vanness DJ

ISSUE PANELS

Mon., May 21, 3:45 PM - 4:45 PM

IP3: The Machine Learning Debate: Panacea or the New Alchemy?

Ramagopalan S, Briggs A, Capkun G, **Wasiak R**

Tues., May 22, 11:00 AM - 12:00 PM

IP9: Lies, Damned Lies and Cost-Effectiveness: Open-Source Models are Essential if Cost-Effectiveness Analyses are to be Widely Accepted

Hawkins N, Arnold RJG, **Caro JJ**

PODIUM PRESENTATIONS

P2: ADDICTION AND MENTAL HEALTH STUDIES
Mon., May 21, 11:00 AM - 12:00 PM

MH1: Descriptive Results from the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ) Validation Study

Coyne KS, Barsdorf AI, Poon J, **Maziere JA**, Pierson RF, Schnoll S, Butler SF, Farrar JT, Porter LN, Franks Jr MJ

P3: MEDICAL DEVICE AND DIAGNOSTICS STUDIES
Mon., May 21, 3:45 PM - 4:45 PM

MD4: Payer Coverage and Evidence Requirements for Oncology Liquid Biopsy Testing in the United States: Current State and Filling the Gaps

Spinner DS, Faulkner EC, Ringo MC, Mihos MC, Joines J

P7: CANCER STUDIES
Tues., May 22, 11:00 AM - 12:00 PM

CN4: Projecting Overall Survival (OS) with Immuno-Oncology (IO) Treatments: Application of Alternative Approaches in Metastatic Merkel Cell Carcinoma (MMCC)

Proskorovsky I, Lanitis T, Ambavane A, Hunger M, Bharmal M, Zheng Y, Phatak H

P13: CONCEPTUAL PAPERS
Wed., May 23, 8:30 AM - 9:30 AM

CP3: Assessment-Time Bias: Statistical Approaches to Adjusting for Between-Trial Differences in the Schedule of Assessment for Disease Progression in Immuno-Oncology Trials

Kapetanakis V, Schlichting M, Stevens JW, **Prawitz T**, Kearney M, Phatak H, **Benedict A**, Bharmal M

KEY: **Bold Black** = *Evidera staff member* | **Bold Purple** = *PPD staff member*

POSTERS

SESSION I
PMS: MUSCULAR-SKELETAL DISORDERS
Mon., May 21, 8:30 AM - 2:00 PM

PMS34: Cost-Effectiveness Analysis of Biologic Therapies for Treatment of Psoriatic Arthritis

Gharaibeh M, **Folse HJ**, Stolshek B, **Zou D, Harris M**, Collier D, Malone DC

SESSION I
PND: NEUROLOGICAL DISORDERS
Mon., May 21, 8:30 AM - 2:00 PM

PND5: The Clinical Value of Early Diagnosis Tests for the Long-Term Management of Dementia

Tafazzoli A, Kansal A

SESSION I
PND: NEUROLOGICAL DISORDERS
Mon., May 21, 8:30 AM - 2:00 PM

PND20: Modeled Survival Gains of Patients with Cystic Fibrosis (CF) Aged > 12 Years Homozygous for the F508DEL Mutation Treated with the CF Transmembrane Conductance Regulator Modulator (CFTRM) Tezacaftor/Ivacaftor (TEZ/IVA)

Lopez A, Suthoff E, **Chandler C**, Liou T, Konstan M, **Pelligra C, Ward A**, Rubin J, McGarry L

SESSION I
PRM: RESEARCH ON METHODS
Mon., May 21, 8:30 AM - 2:00 PM

PRM1: Converting EORTC QLQ-C30 Scores to EQ-5D Utility Scores in the Brigatinib Alta Study

Kawata AK, Lenderking WR, Eseyin OR, Kerstein D, Huang J, Huang H, Lin HM

SESSION I
PRM: RESEARCH ON METHODS
Mon., May 21, 8:30 AM - 2:00 PM

PRM87: Psychometric Validation of the 1-Month Recall Uterine Fibroid Symptom and Health-Related Quality-of-Life Questionnaire

Coyne KS, Harrington A, **Currie BM, Chen J**, Gillard P, Spies JB

SESSION I
PRM: RESEARCH ON METHODS
Mon., May 21, 8:30 AM - 2:00 PM

PRM120: What's the Burden of Burden of Illness Reviews?

Betts MB, Nambiar S, **Khankhel Z, Nejati M**, Lewis J, **Cichewicz A, Snook K, Martin AL**

SESSION I
PRM: RESEARCH ON METHODS
Mon., May 21, 8:30 AM - 2:00 PM

PRM121: Assessing Cellulite Severity: Method for Assessing Reliability of a New Clinician-Reported and a New Patient-Reported Photonumeric Scale

Kirby MT, McLane MP, **Lenderking WR**, Bender R, **Chen J**, Hurley D, **Knoble N**, Liu G, Davidson JA

SESSION II
PCP: CONCEPTUAL PAPERS
Mon., May 21, 3:30 PM - 7:30 PM

PCP24: Projecting Survival with Cure Mixture Models: When are the Data Mature Enough for Reliable Analysis?

Ishak KJ, Villalobos CF, Proskorovsky I

SESSION II
PHS: HEALTH SERVICES
Mon., May 21, 3:30 PM - 7:30 PM

PHS17: An Economic Evaluation of Conservative Management and Cryotherapy in Patients with Localized Prostate Cancer

Shah S, Young HN, Cobran EK

SESSION II
PRS: RESPIRATORY-RELATED DISORDERS
Mon., May 21, 3:30 PM - 7:30 PM

PRS38: Analysis of Social Media Data Using Qualitative Methods: Understanding Preferences and Perceptions of Biologic Medications among Patients with Severe Asthma

Gelhorn HL, Ross M, Balantac ZL, Merinopoulou E, Booth A, Cutts K, Fox KM, Ambrose C, **Cox A**

SESSION II
PRS: RESPIRATORY-RELATED DISORDERS
Mon., May 21, 3:30 PM - 7:30 PM

PRS39: Psychometric Analyses of PROs in Bronchiectasis

Speck RM, Bender RH, Gerlinger C, Filonenko A

SESSION III
PIH: INDIVIDUAL'S HEALTH
Tues., May 22, 8:30 AM - 2:00 PM

PIH46: Changes in FDA Post-Marketing Commitments to Support the Pregnancy and Lactation Labeling Rule

Covington D, Buus R, **Mabe B**

SESSION III
PMH: MENTAL HEALTH
Tues., May 22, 8:30 AM - 2:00 PM

PMH48: Quality of Life and Functional Impairment Results: A Prospective Real-World Dyskinesia Screening Study and Registry in Patients Taking Antipsychotic Agents

Caroff S, Cutler A, **Lenderking WR, Yeomans K, Shalhoub H**, **Ford A**, Yonan C

SESSION IV
PCN: CANCER
Tues., May 22, 3:30 PM - 7:30 PM

PCN159: A Comparison of Patient and Caregiver Worries for Acute Myeloid Leukemia

Oakes AH, **Seo J**, Janssen E, O'Donoghue B, Bridges JF

SESSION IV
PGI: GASTROINTESTINAL DISORDERS
Tues., May 22, 3:30 PM - 7:30 PM

PGI28: The American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index-Daily Diary (ANMS GCSI-DD): Assessing the Content Validity in Patients with Idiopathic or Diabetic Gastroparesis

Revicki DA, Gleeson S, Speck R, Puelles J, Kuo B, Camilleri M, Parkman HP

SESSION V
PIN: INFECTION
Wed., May 23, 8:30 AM - 1:30 PM

PIN24: Hepatitis B Virus (HBV) Vaccine in Pregnancy and Impact on Pregnancy Outcome

Covington D, Kaydo S, **Veley K**

SESSION V
PSY: SYSTEMIC DISORDERS/ CONDITIONS
Wed., May 23, 8:30 AM - 1:30 PM

PSY55: Cost-Effectiveness Analysis of Daratumumab, Lenalidomide, and Dexamethasone (DRD) and Daratumumab, Bortezomib, and Dexamethasone (DVD) versus Standard of Care in Relapsed or Refractory Multiple Myeloma (RRMM)

Pelligra C, Guo S, Parikh K, **Zhang S, Krotneva M**, Onyekwere U, Clancy Z

SESSION V
PSY: SYSTEMIC DISORDERS/ CONDITIONS
Wed., May 23, 8:30 AM - 1:30 PM

PSY89: Payer Coverage of Exercise Regimens for Treating Lower Back Pain in the United States: Current Landscape and Opportunities to Address the Burden

Spinner DS, Leverette MH, Green EB, **Ringo MC, Mihos MC**, Browner BD, **Faulkner EC**

KEY: **Bold Black** = *Evidera staff member* | **Bold Purple** = *PPD staff member*

Upcoming Presentations

The American Thoracic Society International Conference

May 18-23, 2018; San Diego, CA, USA

POSTERS

Concordance Between Health Care Utilization and Symptom-Defined Exacerbations in Patients with COPD: Results from the Acute Exacerbation and Respiratory InfectionS (AERIS) Study

Sung R, Collier S, Devaster J, **Leidy NK,** Ostridge K, Staples J, Locantore N. Wilkinson T, Tal-Singer R, Miller BE, AERIS Study Group

Incidence of Chronic Obstructive Pulmonary Disease Symptom-Defined Exacerbations: Exploratory Analysis from a Long-Term Open-Label Active-Controlled Safety Trial of Nebulized Glycopyrrolate/eFlow® CS

Kerwin EM, Ganapathy V, **Murray L,** Rajagopalan K

Respiratory Symptoms and Health Status in Patients with Chronic Obstructive Pulmonary Disease (COPD): Results from the Acute Exacerbation and Respiratory InfectionS (AERIS Study)

Sung R, Collier SD, Devaster J, **Leidy NK,** Ostridge K, Staples KJ, Locantore N, Wilkinson T, Tal-Singer R, Miller B, AERIS Study Group

What Symptomatic Patients with Asthma and Chronic Obstructive Pulmonary Disease (COPD) Find Important in Their Maintenance Inhaler Therapy: A Focus Group Study

Hanania N, **Hawken N,** Gilbert I, Martinez F, Fox K, **Ross M, Duenas A, Kawata A, Cooper O, Tervonen T**

WOCN 50TH Annual Conference

June 3-6, 2018; Philadelphia, PA, USA

POSTER

Cost-effectiveness of a Ceramide-infused Skin Barrier among Medicare Enrollee Patients in the United States Who Have Recently Undergone Ostomy

Berger A, Oguz M

American Headache Society 60th Annual Scientific Meeting

June 28-July 1, 2018; San Francisco, CA, USA

POSTER

Psychometric Validation of the MSQv2.1 ePRO for Use in Patients with Episodic and Chronic Migraine

Speck RM, Shalhoub H, Ayer DW, Ford J, Wyrwich KW, Bush EN

ISOQOL 25TH Annual Conference

October 24-27, 2018; Dublin, Ireland

WORKSHOP

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

Hareendran A, Skalicky A, Magasi S

Recent Presentations

APA Annual Meeting

May 5-9, 2018; New York City, NY, USA

POSTERS

Characteristics of Patients with Mood Disorders Taking Antipsychotics: Data from Depression and Bipolar Support Alliance

Deetz I, **Ganz M, Shah S,** Doederlein A, DePeralta D, Yonan C

Results of a Depression and Bipolar Support Alliance Survey: Focused Analysis of Tardive Dyskinesia in Patients with Mood Disorders

Richmond L, Deetz I, **Ganz M, Shah S,** Doederlein A, DePeralta D, Yonan C

AMCP Annual Meeting

April 23-26, 2018; Boston, MA, USA

POSTER

A Prospective Real-World Dyskinesia Screening Study and Registry in Patients Taking Antipsychotic Agents: Quality of Life and Functional Impairment Results

Caroff S, Cutler A, **Lenderking WR, Yeomans K, Shalhoub H, Ford A**, Yonan C

AAN Annual Meeting 2018

April 21-27, 2018; Los Angeles, CA, USA

POSTERS

Capturing Latency in Cognitive Symptoms for People with Significant Memory Concern

Tafazzoli A, Kansal A, Krotneva M, Weng J, Ishak KJ

RE-KINECT: A Prospective Real-World Dyskinesia Screening Study and Registry in Patients Taking Antipsychotic Agents: Patient Demographics

Tanner C, Cutler A, Caroff S, **Lenderking WR, Yeomans K, Shalhoub H,** Ross L, Yonan C

Simulation Study on Differences in Alzheimer Disease (AD) Cooperative Study–Preclinical Alzheimer Cognitive Composite (ADCS-PACC) Based on Long-Term Clinical Outcomes

Kansal A, Stern S, Keenan A

DIA Europe 2018

April 17-19, 2018; Basel, Switzerland

POSTERS

Evaluating Long Term Effects of Gene Therapy Medicinal Products (GTMP) – What About the Patients' Experience?

Hareendran A, Dias-Barbosa C, McCormick J, Boren J

Risk Minimization Evaluation: A Patient-Centric Framework for Evaluation Integrating Qualitative and Quantitative Methods

Rubino A, Hareendran A

11TH International Symposium on Pneumococci & Pneumococcal Diseases

April 15-19, 2018; Melbourne, Australia

POSTER

Implementing the 2014 ACIP Pneumococcal Conjugate Vaccination Recommendations for US Adults 65+ in the Era of Electronic Health Records

Snow V, Vietri J, **Berger A,** Chilson E, Sato R

KEY: **Bold Black** = *Evidera staff member* | **Bold Purple** = *PPD staff member*

SAS Global Forum 2018

April 8-11, 2018; Denver, CO, USA

SPEAKER

A General SAS® Macro to Implement Optimal N:1 Propensity Score Matching within a Maximum Radius

Fraeman K

SIRS 2018

April 4-8, 2018; Florence, Italy

POSTER

Impact of Side Effects due to Second-Generation Antipsychotics on the Functioning of Patients with Schizophrenia: An Observational, Patient Centered, Web Survey

Tandon R, Weiss C, **Lenderking WR, Cooper O, Shalhoub H, Kleinman L, Chen J,** Hartry A, Greene M, Meehan SR, Bouerat Duvold L

American Society for Clinical Pharmacology and Therapeutics (ASCPT) 2018 Annual Meeting

March 21-24, 2018; Orlando, FL, USA

WORKSHOP

Leveraging Novel Simulation Techniques to Incorporate Pharmacometrics in Pharmacoeconomic Models

Caro JJ

World Pharma Pricing and Market Access 2018

March 20-21, 2018; London, UK

PODIUM

Evidence Generation Considerations for Rare Diseases

Navarro E

DIA | MASC 2018

March 19-21, 2018; Rancho Mirage, CA, USA

ORAL PRESENTATION

Innovation in Communications

Cash K, Lippincott R

ACC.18

March 10-12, 2018; Orlando, FL, USA

POSTER

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

World Meeting on Sexual Medicine

February 28-March 3, 2018; Lisbon, Portugal

ORAL PRESENTATION

Bremelanotide Provides Meaningful Treatment Benefits for Premenopausal Women with Hypoactive Sexual Desire Disorder

Koochaki PE, **Revicki DA, Wilson H, Pokrzywinski R,** Jordan R, Lucas J

ISCTM 14TH Annual Scientific Meeting

February 20-22, 2018; Washington, DC, USA

POSTER

Developing Clinically Meaningful Responder Thresholds for Primary Endpoints for Clinical Trials in Premenopausal Women with Hypoactive Sexual Desire Disorder

Revicki DA, Clayton AH, Stouch BC, Portman DJ, Kingsberg SA, DeRogatis LR, Jordan R

ORAL PRESENTATION

Clinical Outcome Assessment Endpoints for Rare Diseases: Challenges and Methods for Clinical Trials

Revicki DA

International Pharmaco-Economic Conference on Alzheimer's Disease

February 15-16, 2018; Paris, France

ISSUE PANEL

Key Challenges for Modeling Alzheimer's Disease

Getsios D

ECCO Annual Congress 2018

February 14-17, 2018; Vienna, Austria

POSTERS

Early Use of Vedolizumab versus Infliximab in Biologic-Naive Patients with Ulcerative Colitis: A Real-World Analysis of Healthcare Utilisation

Patel H, Khalid JM, **Shah S, Shah R, Berger A**

Real-World Drug Treatment Costs for Ulcerative Colitis and Crohn's Disease Patients Treated with Vedolizumab vs Anti-TNFα: Results from a German Retrospective Chart Review Study

Campbell-Hill S, **Stein D, Soni M, Coombs C,** Ratsch B, Khalid JM, Minda K

Vedolizumab Outcomes in Real-World Bio-Naive Ulcerative Colitis and Crohn's Disease Patients (EVOLVE) in Canada: Interim Results

Bressler B, Greenup AJ, **Bassel M, Stein D, Soni M,** Radulescu G, Neish C, Khalid JM, Demuth D

Genitourinary Cancers Symposium

February 8-10, 2018; San Francisco, CA, USA

POSTERS

Overall Survival and Treatment Patterns among Real-World Patients with Locally Advanced or Metastatic Urothelial Carcinoma Treated with First-Line Therapy

Simeone JC, Nordstrom BL, Patel K, Klein AB, Horne L

Real-World Survival and Treatment Patterns of Patients with Locally Advanced or Metastatic Urothelial Carcinoma Treated with Second-Line Therapy after Platinum-Based Chemotherapy

Simeone JC, Nordstrom BL, Patel K, Klein AB, Horne L

2018 Sentinel Initiative Annual Public Workshop

February 7, 2018; Bethesda, MD, USA

WORKSHOP

Use of Mini-Sentinel Tools to Assess Cardiovascular Outcomes with Treatment of Overactive Bladder

Nordstrom B

Advanced Pharma Analytics Europe 2018

January 30-31, 2018; London, UK

PODIUM

Machine Learning (ML) for Late Stage Development: Realising the Potential

Cox A

ISSUE PANEL

Broadening Horizons for Real-World Evidence Analytics

Cox A

KEY: **Bold Black** = *Evidera staff member* | **Bold Purple** = *PPD staff member*

Recent Publications

Althof SE, Rosen RC, ***Revicki DA***. Linguistic and Cultural Validation of Patient-Reported Outcomes Used in Clinical Trials. *J Sex Med*. 2018 Feb;15(2):115-117. doi: 10.1016/j.jsxm.2017.11.017.

Ambavane A, Lindahl B, Giannitis E, ***Roiz J***, Mendivil J, Frankenstein L, Body R, Christ M, Bingisser R, Alquezar A, Mueller C; TRAPID-AMI investigators. Economic Evaluation of the One-Hour Rule-Out and Rule-In Algorithm for Acute Myocardial Infarction using the High-Sensitivity Cardiac Troponin T Assay in the Emergency Department. *PLoS One*. 2017 Nov 9;12(11): e0187662. doi: 10.1371/journal.pone.0187662.

Bacci ED, DeLozier AM, Lin CY, Gaich CL, Rooney T, Hoffman R, Wyrwich KW. Psychometric Properties of Morning Joint Stiffness Duration and Severity Measures in Patients with Moderately to Severely Active Rheumatoid Arthritis. *Health Qual Life Outcomes*. 2017 Dec 6;15(1):239. doi: 10.1186/s12955-017-0813-7.

Bacci ED, DeLozier AM, Lin CY, Gaich CL, Zhang X, Rooney T, de Bono S, Hoffman R, Wyrwich KW. Psychometric Properties of the Single-Item Measure, Severity of Worst Tiredness, in Patients with Moderately to Severely Active Rheumatoid Arthritis. *Health Qual Life Outcomes*. 2017 Dec 6;15(1):237. doi: 10.1186/s12955-017-0807-5.

Bacci ED, O'Quinn S, ***Leidy NK, Murray L, Vernon M***. Evaluation of a Respiratory Symptom Diary for Clinical Studies of Idiopathic Pulmonary Fibrosis. *Respir Med*. 2018 Jan; 134:130-138. doi: 10.1016/j.rmed.2017.11.011.

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Burger CD, Pruett JA, Lickert CA, ***Berger A, Murphy B***, Drake W 3rd. Prostacyclin Use Among Patients with Pulmonary Arterial Hypertension in the United States: A Retrospective Analysis of a Large Health Care Claims Database. *J Manag Care Spec Pharm*. 2018 Mar;24(3):291-302. doi: 10.18553/jmcp.2017.17228.

Calvert M, Kyte D, Mercieca-Bebber R, Slade A, Chan AW, King MT; the SPIRIT-PRO Group, Hunn A, Bottomley A, Regnault A, Chan AW, Ells C, O'Connor D, ***Revicki D***, et al. Guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols: The SPIRIT-PRO Extension. *JAMA*. 2018 Feb 6;319(5):483-494. doi: 10.1001/jama.2017.21903.

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Cather JC, Ryan C, Meeuwis K, Potts Bleakman AJ, Naegeli AN, Edson-Heredia E, Poon JL, Jones C, Wallace AN, Guenther L, Fretzin S. Patients' Perspectives on the Impact of Genital Psoriasis: A Qualitative Study. *Dermatol Ther (Heidelb)*. 2017 Dec;7(4):447-461. doi: 10.1007/s13555-017-0204-3.

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Evidera's Eric Faulkner Collaborates with ARM and NAMCP on a Pivotal Study of Patient Access Drivers for Regenerative and Advanced Therapies

Congratulations to Eric Faulkner, MPH, Vice President and Executive Director, Real-World Value and Strategy, Center of Excellence - Precision and Transformative Technology, on his collaboration with The Alliance for Regenerative Medicine (ARM) and the National Association of Managed Care Physicians (NAMCP) on a study of payer and provider medical director perspectives on value demonstration and reimbursement for regenerative and advanced therapies.

The study publication, "Ensuring Patient Access to Regenerative and Advanced Therapies in Managed Care: How Do We Get There?," was announced in a joint ARM and NAMCP press release earlier this year. The assessment identifies various challenges and posits possible solutions to ensure the appropriate integration of these high-value therapies into the current U.S. health care system. The study also takes a look at various alternative payment and financing models to enable sustainable patient access to these products.

As lead author for the publication, Eric Faulkner commented, "This is a critical time for dialogue between regenerative and advanced therapy manufacturers, managed care, and other stakeholders. Our health system is continuously seeking innovations that have the potential to transform patient outcomes and truly 'move the needle.' Regenerative and advanced therapies have such potential, but they will enter global health systems that are ill-prepared to receive truly transformative therapies. This paper is part of the vanguard of early global dialogue to help bridge this gap and help prepare us for novel technologies that may alter our expectations for therapy development and patient care."

"This study highlights Evidera's commitment to help optimize access to health technologies with significant potential to improve patient health – such as precision medicines; cell, gene, and regenerative therapies; specialty treatments; novel biologics; and, e-connective technologies," stated Jon Williams, President of Evidera. "These therapies often have more complex value demonstration, market access, and commercial issues as compared to conventional pharmaceuticals. Recognizing these differences, Evidera's team of scientists and consulting executives are focused on developing actionable novel and custom-tailored approaches to support these technologies."

Read the full press release at alliancerm.org for a more detailed overview and summary of key learnings of the study. The full study publication is accessible in the *Journal of Managed Care Medicine* (namcp.org/journals/JMCMArm.pdf).

Evidera's Dr. Colleen A. McHorney Honored with NQF Innovation Challenge Award

Colleen A. McHorney, PhD, Senior Research Leader, Patient-Centered Research at Evidera, was among the five winning entries of the National Quality Forum (NQF) 2017 Measure Incubator™ Innovation Challenge.

NQF announced five winning entries for their 2017 contest for innovative and agile approaches for performance measurement that incorporate one or more Principles for Making Health Care Measurement Patient-Centered. The 2017 Innovation Challenge was part of NQF's Measure Incubator™ — an initiative that nurtures the development of needed measures by connecting organizations interested in specific measure concepts with measure development experts, financial and technical resources, and data. There were 32 entries in total.

Dr. McHorney received this award for her contribution to ongoing work, in collaboration with a biopharmaceutical company, that focused on the role of patients and caregivers in conceptualizing oncology quality-of-care measures that address patient and caregiver concerns, values, and preferences for oncology care across the entire treatment pathway. Dr. McHorney presented on this topic on January 23, 2018, during NQF's Learning Collaborative Patient-Centered Measurement Webinar Series (available on-demand at www.qualityforum.org).

"It is an honor to be recognized with an NQF Innovation Challenge award," stated Dr. McHorney. "Patient and caregiver involvement is extremely important in the conceptualization and development of new patient-centered quality-of-care measures. It is critical to not only measure patient outcomes but also patient priorities, values, and preferences for processes and outcomes of their oncology care. With the increasing focus on patient-centered research and the immense growth in novel cancer therapies, our work in this area is even more critical. Having an organization like NQF foster and recognize this type of patient-centered research is very fulfilling."

Evidera has expanded its patient-centered research services to provide clients with new and innovative approaches to more effectively gather and incorporate patient perspectives into drug-development programs. This award is a testament to our dedication to ensuring the patient's voice is heard throughout the drug development lifecycle.

Complete details on NQF's 2017 Innovation Challenge, including all the award winners and their entry topics, can be found on their website (www.qualityforum.org).

WELCOME TO NEW SENIOR STAFF

Donny Chen, MBA

Executive Director, Registries and Prospective Studies, Real-World Evidence

Donny Chen brings 19 years of global, peri- and post-approval clinical research experience to Evidera, with specific expertise in observational research, pragmatic trials, and health economics and outcomes research (HEOR) studies. Prior to joining Evidera, Mr. Chen worked for PPD, Evidera's parent company, for over seven years, most recently as the senior director of project management. Before that, he was a senior project manager at ICON Clinical Research - a global contract research organization; a senior manager at Ovation Research Group - a boutique medical affairs consultancy; and, a researcher in breast cancer at the University of Chicago Medical Center. His therapeutic experience includes cardiology, hematology, immunology, infectious diseases, neurology, oncology, rheumatology, and metabolic and respiratory indications, in both adult and pediatric populations and including rare diseases. Mr. Chen has been published in peer-reviewed journals and has contributed to 30+ abstracts, posters, and speaking engagements at scientific conferences. Mr. Chen graduated Phi Beta Kappa from the University of Chicago with concentrations in economics and pre-medicine. He received his MBA from the University of Chicago Booth School of Business with concentrations in finance and strategy.

Sohan Deshpande, MSc, M-Tech

Research Scientist, Meta Research

Mr. Deshpande brings valuable experience in leading and disseminating qualitative and quantitative systematic reviews, as well as conducting health technology assessments of research evidence. Prior to joining Evidera, Mr. Deshpande worked at Kleijnen Systematic Reviews (KSR) Ltd, a National Institute for Health and Care Excellence (NICE) Evidence Review Group (ERG). In this role, he provided critical evaluations of single technology appraisals (STA) and production of ERG reports for NICE committee meetings, consequently gaining a deep understanding of how NICE and reimbursement decisions are made. Mr. Deshpande's technical expertise encompasses systematic reviews involving direct/indirect meta-analysis, network meta-analysis, burden-of-disease assessments, and focused literature reviews. He has wide therapeutic-area knowledge, having worked on projects with a wide range of diagnostic and treatment interventions for NICE, the Scottish Medicines Consortium, the National Institute for Health Research, and other commissioners, including pharmaceutical companies across disease topics such as oncology, incontinence, hypertension, diabetes, cardiovascular diseases, HIV, immunology, and chronic obstructive pulmonary disease. His work has been published in a variety of top-tier, peer-reviewed journals. His experience also includes work for, and several publications with, the Cochrane Wounds Group. Mr. Deshpande received an MSc in international health sciences from the University of York, and a master of technology (M-Tech) and a bachelor of technology (B-Tech) in biotechnology from Dr. D.Y. Patil University, Navi Mumbai.

Theo J. Hoofwijk, MD

Vice President and General Manager
Peri- and Post-Approval Interventional Studies

Dr. Hoofwijk is an experienced clinician, researcher, and strategist providing senior level strategy and direction for Evidera's interventional study practice, ensuring scientific and operations excellence are aligned. He brings more than 20 years of experience working within CROs and the pharmaceutical industry, including a wealth of experience in drug safety, clinical drug development, and medical affairs research in both local country operations and the corporate pharmaceutical environment. During his career, he has led strategic drug development activities for pharmaceutical customers and managed global programs in the cardiovascular and gastroenterology therapeutic areas. His contributions to the field include developing, leading, and supporting clinical development programs in functional bowel diseases, dyslipidemia, acute coronary syndromes, coronary artery disease, heart failure, hypertension, Type 2 diabetes mellitus, and orthotopic liver transplantation. Prior to joining Evidera, Dr. Hoofwijk was employed by Quintiles (now IQVIA) where he held the positions of global medical head cardiovascular/metabolic, therapeutic strategy lead, regional chief medical officer EMEA, and head of strategic drug development APAC. Dr. Hoofwijk received his medical degree from the University of Amsterdam.

Paul Juneau, MS

Lead Statistician, Real-World Evidence

Mr. Juneau has worked as a statistician for over 28 years supporting research in the biopharmaceutical industry, spanning target identification, product discovery, toxicology, development, and manufacturing, as well as pharmacoeconomics and outcomes research. He has experience in the design, analysis, and reporting of studies related to arthritis and inflammatory diseases; autoimmune disorders; bacterial, fungal, and viral infectious diseases; cancer; dermatological diseases; diabetes; dyslipidemia; hypertension; obstetrics; osteoporosis; opioid addiction; pain; psychiatric disorders; and, thrombosis. Mr. Juneau's primary objective as a statistician is to assist internal researchers and external clients so that they can make critical decisions and tell compelling value stories about new therapies for a wide array of indications. He has contributed to numerous publications, written a book chapter on nonparametric statistical methods, presented at conferences throughout the U.S. and in Europe, and is the author of some award-winning SAS code that has been distributed to researchers on several continents. Prior to joining Evidera, Mr. Juneau served as a senior statistician for IBM Watson Health for seven years and worked at two large biopharmaceutical companies for approximately 20 years. He received his MS in mathematical statistics from The Ohio State University.

Katie Mercaldi, MPH
Senior Data Analyst, Real-World Evidence

Ms. Mercaldi has over 10 years of experience in the health care industry and has served as both an epidemiologist and analyst on a variety of research studies, focusing mainly on retrospective observational studies of insurance claims data and other large, relational health care databases. She has experience in a variety of study types, including treatment patterns, comparative analyses, matched cohort designs, safety outcomes, and cost/utilization related to treatment and/or disease. She has extensive experience using SAS programming, and her responsibilities include preparing, managing, and analyzing research datasets, as well as assisting in the development of study documents. She has worked in a number of disease and therapeutic areas, including diabetes and metabolism, hospital-acquired infection, atrial fibrillation, and oncology, with published works in major industry journals. Prior to joining Evidera, Ms. Mercaldi was a biostatistician and epidemiologist at United BioSource Corporation and was a biostatistician for the Division of Endocrinology, Diabetes, and Metabolism at Beth Israel Deaconess Medical Center in Boston where she provided statistical and analytic support for several epidemiologic and clinical studies. Ms. Mercaldi earned her MPH in biostatistics and epidemiology from the Boston University School of Public Health and her BA in mathematics and statistics from Boston University.

Delphine Saragoussi, MD, MScPH
Research Scientist, Real-World Evidence

Dr. Saragoussi is a physician specialized in public health and social medicine, with a diverse history of over 15 years of applied experience in epidemiology and pharmacoepidemiology and a deep understanding of strategic, real-world evidence needs throughout the drug development process. She has developed and implemented various peri- and post-approval, real-world evidence plans to support successful market access, with expertise in the collection of primary data and the use of electronic databases (European and U.S. claims and electronic medical records databases); burden of illness evaluations; treatment pattern descriptions; PRO validations; and, real-world effectiveness studies. Dr. Saragoussi is also well versed in the design of post-authorization safety studies to meet European regulatory and pharmacovigilance evidence needs. Prior to joining Evidera, Dr. Saragoussi served as a global therapy area lead in the real-world evidence and epidemiology department at Lundbeck where she led psychiatry and neurology research. Additionally, she has also worked in academic research units, semi-private health insurance companies, and the French Drug Agency with a focus on occupational health, nutrition, genetic epidemiology, and psychiatric epidemiology. She trained in medicine at the University of Paris V Descartes, specializing in adult and pediatric endocrinology, genetic disorders, and cardiovascular diseases, and she earned a MScPH in methodology and statistics in biomedical research from the Faculté de Kremlin Bicêtre, University Paris XI. Dr. Saragoussi regularly publishes her works in peer-reviewed journals.

Leigh Ann White, PhD
Senior Director, Market Access Communications

Dr. White has over 20 years of experience in health care, including market access strategy and health economics and outcomes research evidence generation. In her current role, she leads client engagements with a focus on developing product value stories, global value dossiers, and AMCP dossiers. Previously, Dr. White served as an associate director in global market access for Biogen's neuroscience assets, including Alzheimer's disease and amyotrophic lateral sclerosis (ALS). Prior to her tenure at Biogen, Dr. White worked for Analysis Group and Boston Health Economics, conducting health economics and outcomes research for biotechnology clients. She has published systematic reviews, economic models, epidemiology, and health outcomes studies in disease areas such as ALS, multiple sclerosis, pain conditions, psychiatric illnesses, rheumatoid arthritis, and oncology. She is adept at organizing efforts to seek payer advice through advisory boards and more formal early scientific advice procedures, as well as communicating product value from cost-effectiveness and budget impact model results. Dr. White draws on her deep experience to provide clients with communications services that fit a product's stage of clinical development and overall market access strategy. Dr. White earned a PhD in health economics from the Johns Hopkins Bloomberg School of Public Health, an MA in demography (population studies) from Georgetown University, and a BA in mathematics from Sweet Briar College.

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