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NOVEMBER 2017



Redefining Drug Development

04

The Drive Toward Pragmatism in Randomized Trials
Are We There Yet?

15

21ST Century Cures Act
Innovation, Breakthroughs, and Research in
Under-Represented Populations

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Access Options for Investigational Products
Key Considerations

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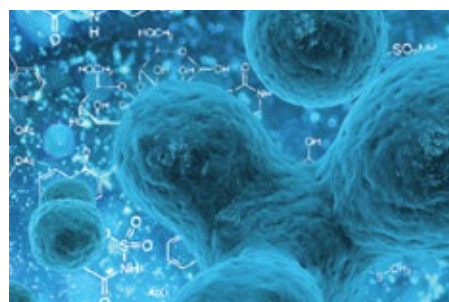
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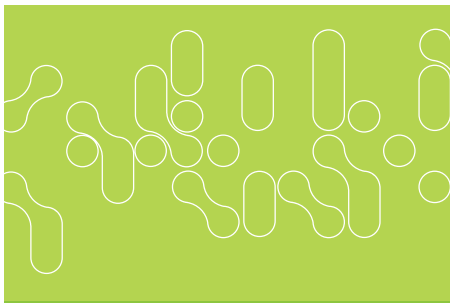
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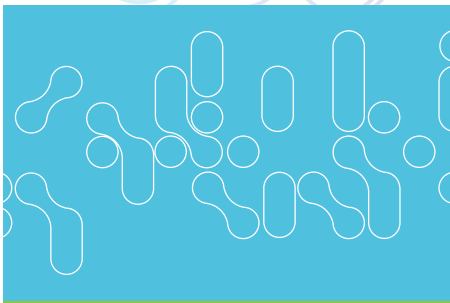
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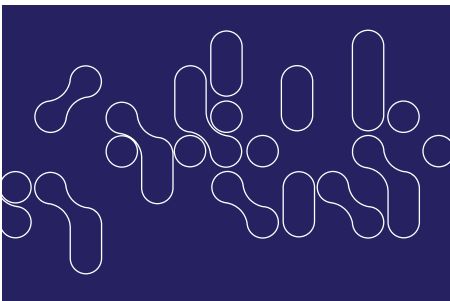
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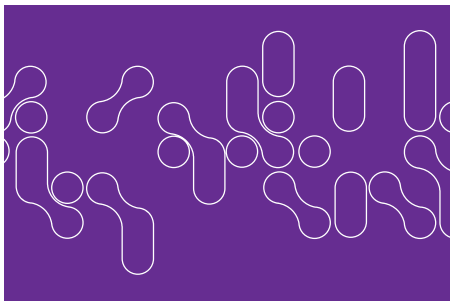
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The Drive Toward Pragmatism in Randomized Trials: Are We There Yet?

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What's Fueling the Drive Toward Pragmatism?

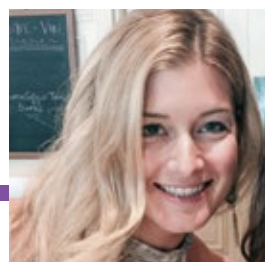
Suggestions on the need for pragmatism in clinical trials arose at least a half century ago, forming the backdrop for some of the earliest examples, such as the Physicians' Health Study and the GISSI trial, initiated in the 1980s. Yet evidence shows a trend since that time toward increasing complexity in trials¹ rather than widespread adoption of pragmatism. In a contravening trend, though still comprising only a small minority of the overall trial output globally (*Figure 1*), pragmatic trials have been the subject of increased attention and focused efforts of key stakeholders in the healthcare system. Among the factors contributing to the recent resurgence of dialogue around pragmatism, we think three factors have been crucial.

Increasing Capabilities in Real-World Evidence (RWE)

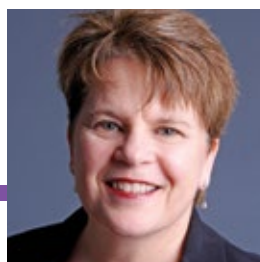
The dawning of the Information Age spawned a large and diverse impact on the healthcare system, including various dimensions of drug development and healthcare, and has enabled the possibility of more real-world evidence-based decisions on the part of drug developers, regulatory agencies, clinicians, health plans, and patients. The rapid and continuous development of information infrastructures and capabilities has resulted in an explosion in the amount and quality of real-world data (RWD) and linkages that have expanded the possibilities for how RWD can be built into RWE to inform decisions, creating a learning healthcare system. Conventional randomized controlled trials (RCTs), sometimes called explanatory trials, remain the gold standard for regulatory submissions for marketing authorizations across the globe, however, they come with a number of important costs and limitations. This has initiated conversations about the need for additional research with a more pragmatic focus designed to answer a somewhat different set of questions directed at real-world effectiveness and safety of interventions. **The goal has shifted to not only bringing to market safe and efficacious interventions, but those for which enough evidence exists that patients will ask, providers will prescribe, and payers will pay.** To meet this goal effectively, RWE is needed throughout the development cycle. Importantly, regulators including the U.S. Food and Drug Administration (FDA) and



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the European Medicines Agency (EMA), as well as other stakeholders such as the National Institutes of Health (NIH) and the Patient-Centered Outcomes Research Institute (PCORI), are active participants in a number of efforts aimed at incorporating RWE – including from pragmatic trials – into regulatory decision making.

Increased Attention to Patient Centricity

A renewed focus on patients and their involvement in healthcare, treatment decisions, and increasingly in designing research is also driving discussions of the role of RWE and pragmatic trials. We have moved from patients being viewed as recipients of healthcare interventions to being participants in the entirety of the healthcare spectrum. People are taking a much more proactive role in their healthcare choices, and technology has enabled patient empowerment, with patients now looking to find the right information at the right time. This search for information initiated by patients moves throughout the healthcare enterprise and has helped highlight existing evidence gaps that have exposed the necessity of generating and integrating RWE into the healthcare paradigm.

Limitations of RCT Evidence to Support Healthcare Decisions and Market Access

A third key factor relates to the recognition of the loss of both efficiency and knowledge that occurs when clinical trials are conducted outside of routine care settings. There is an inherent tradeoff that arises between RCT design choices aimed at enhancing internal validity with those more pragmatic choices that would aid generalizability.

For example, registration trials increasingly tend to enroll relatively small samples of highly selected patients at sites with experienced investigators under ideal conditions, and collect large amounts of very specific data that are often not a routine part of clinical care. A spectrum of increasingly complex design features are being implemented primarily to 1) enhance internal validity, 2) maximize the chance of detection of efficacy signals when a true effect of the intervention exists, and 3) inform understanding of the biological basis of a treatment effect. However, such design features tend to result in high

A renewed focus on patients and their involvement in healthcare, treatment decisions, and increasingly in designing research is also driving discussions of the role of RWE and pragmatic trials.

costs and the inclusion of only a small subset of patients and investigators who often differ substantially from the broader populations of patients and healthcare providers who would eventually be receiving and prescribing the new treatment. The number of registered interventional trials has increased over time,¹ however, most are small with 62% enrolling 100 or fewer participants,¹ and systematic reviews consistently find insufficient evidence to effectively inform the clinical decisions patients and their providers must make. Further, RCTs increasingly study surrogate markers as endpoints, and the relation between those and the outcomes of most importance to patients is not

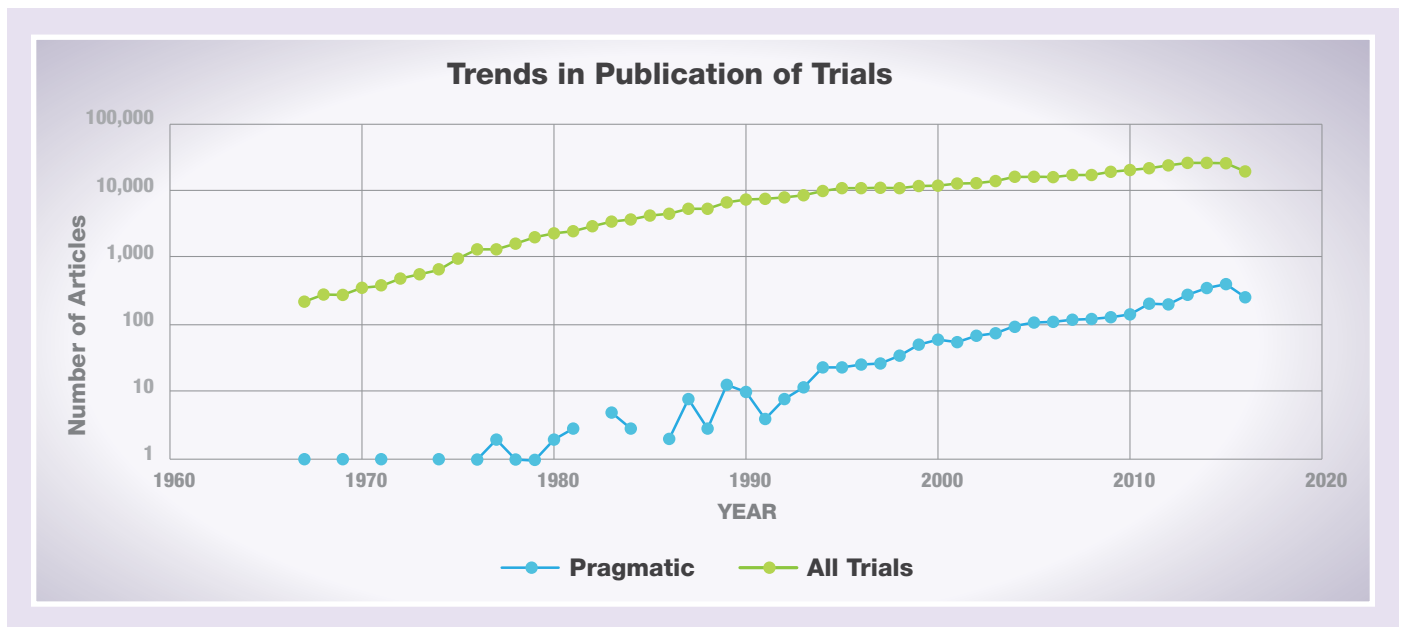








Figure 1. Articles per year from MEDLINE. In blue, resulting from search of the words *pragmatic* or *naturalistic* and *trial* in the title or abstract and tagged as “clinical trial.” In green, articles with *trial* in title or abstract tagged as “clinical trial.” Search is neither sensitive nor specific but meant to demonstrate trends and relative numbers of pragmatic trials versus RCTs in general.

Notably, the relative proportion of trials reported as pragmatic remains low (under 2%), and there is only a hint of a possible increase in the relative proportion of all trials that are reported as pragmatic.

always clear. In order to deliver healthcare interventions that maximize benefit, minimize harm, are cost-effective, and that patients will ask for, providers will prescribe, and payers will pay, it is crucial to understand the balance of benefits and risks of interventions within the context of the complexities of the whole system, including patient populations, provider behaviors, payers, and health systems. Gaps in such information are the rule rather than the exception at the time of market authorization. **Filling such gaps is within the domain of RWE, and the pragmatic trial can be a crucially important mechanism to build the evidence required** to inform decisions and support a transition to a learning healthcare system where RWE is collected and quickly fed back into clinical care, and clinical care itself would inform the further development of medical evidence.

Innovative Approaches to Trials

Achieving evidence needs to inform the move toward a learning healthcare system requires a diverse portfolio of observational and interventional RWE research methods. The case is more compelling than ever for the conduct of more efficient clinical research to enhance the value of healthcare. Innovative approaches to randomized trials can bridge the intersection of observational RWE and the conventional RCT and provide:

-  Patients with better information on treatment options, benefits and risks, and health outcomes that matter to them
-  Patients with multiple conditions the ability to compare the effectiveness of medical treatments
-  Medical providers with evidence needed to more effectively treat patients with multiple conditions and to compare the effectiveness of medical treatments
-  Medical product developers with new insights on both new and existing therapies and unmet medical needs
-  Regulators with better information to understand the effectiveness and safety of medical treatment options in broader patient groups
-  Payers with better information to understand the benefit, risk, and value of medical treatment options

Pragmatic Trials

Pragmatic trials improve generalizability of findings by evaluating health interventions in real-world settings that are more representative of the patients, providers, and health systems in which the intervention will be implemented.² Pragmatic trials draw on the substantial methodological, bias-reducing advantages of random allocation of health interventions combined with the real-world setting of an observational study to provide answers to questions that are relevant to clinical decision making. Randomization can be done at the patient level, or alternative designs such as cluster randomization or cohort multiple randomization can be adopted, particularly if there are concerns that individual level randomization would result in important changes to the routine care process. Due to the increased level of heterogeneity, pragmatic trials must be large enough to be sufficiently powered to detect small to moderate effect sizes.

Large Simple Trials

The large simple trial (LST) is a variation of a pragmatic trial with a sufficiently large sample size (often 10,000 or even 20,000 participants or more) designed to provide evidence on interventions with anticipated small to moderate effects. Characteristics of LSTs include:

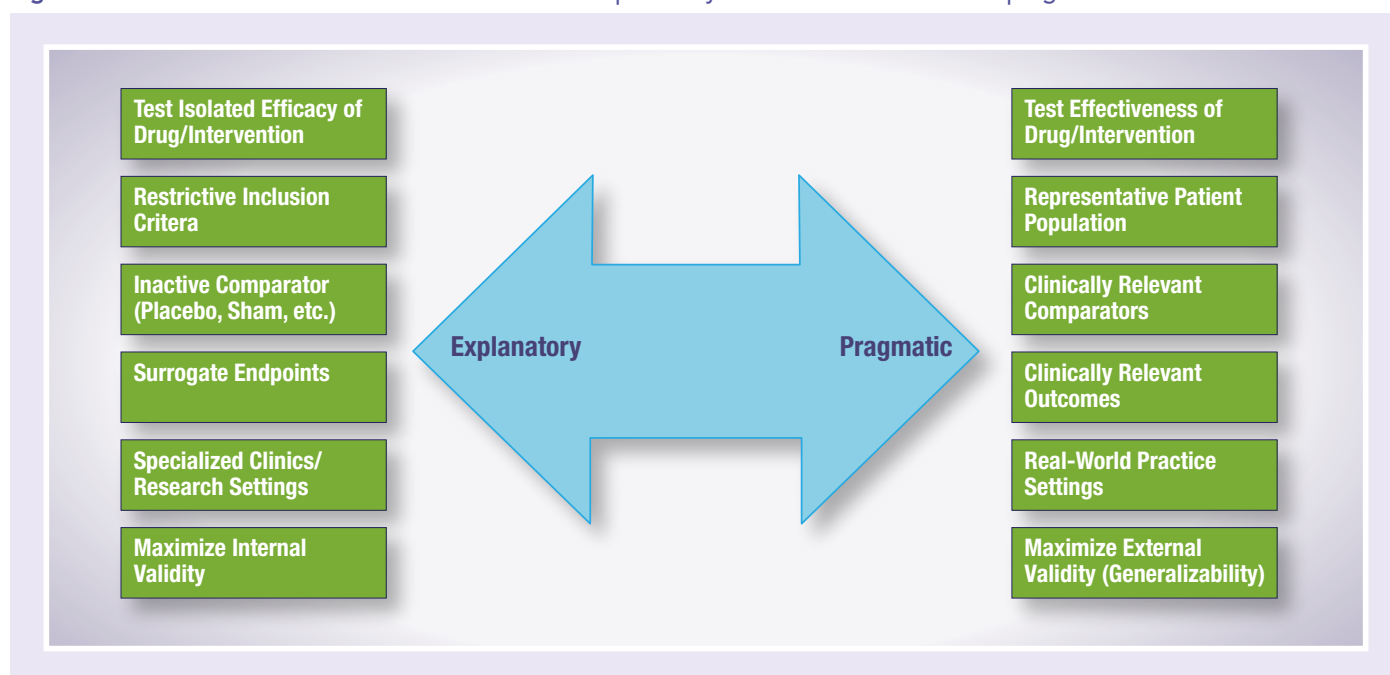
- Broad eligibility criteria
- Simple randomization scheme leading to a diverse patient population and enhanced generalizability
- Clinically meaningful outcomes
- Streamlined design with few or no departures from routine medical care
- Efficient and effective data collection mechanism for capturing outcomes and other relevant information

LSTs are generally Phase IV studies of already marketed health interventions for common health conditions and/or disease prevention, though other applications can be envisioned.

Expanding Body of Pragmatic/ Large Simple Trial Guidance

Only high-quality data can provide substantial evidence needed for regulatory approval, however, there is flexibility in the type of evidence that can be considered, and regulators have made progress in promoting the streamlining of trials.³ In recent years, the FDA has issued guidance on “Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Postapproval Clinical Investigations”⁴ (see Safety section), as well as “Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring,”⁵ and issued a rule modifying investigational new drug safety reporting requirements. Other issues, notably including informed consent procedures, remain unresolved and guidance is

Figure 2. Some core distinctions between traditional explanatory RCTs and trials with more pragmatic elements



needed for institutional review boards (IRBs), sponsors, and investigators to help facilitate the conduct of pragmatic trials under existing regulations while alternatives are considered, such as a risk-based approach for informed consent. Among others, the ongoing NIH Health Care Systems Research Collaboratory supported ABATE Infection cluster randomized trial,⁶ and the Patient-Centered Outcomes Research Institute ADAPTABLE (Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-term Effectiveness) trial⁷ have highlighted considerations related to FDA regulations for informed consent, and should aid in provision of empirical data and knowledge in adapting informed consent processes to this new paradigm of research. The FDA has been actively engaged in a number of multi-stakeholder efforts aimed at the incorporation of RWE into regulatory decision-making.

In Europe, the Good Pharmacovigilance Practice (GVP) Module VIII on Post-Authorisation Safety Studies and Module V on Risk Management plans provide guidance for pragmatic trials. Additional information can be found in The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (Revision 6).⁸

Which Types of Research Questions

Where a trial falls on the explanatory – pragmatic spectrum should emerge from a careful depiction of the overall study question. If the primary aim is to demonstrate and understand the isolated effect of a drug/other intervention (efficacy and safety), tradeoffs aimed at enhancing internal validity will likely take precedence and the trial will likely comprise design choices incorporating more explanatory elements. Pragmatic design features should prevail

Consider Pragmatic Elements to Answer These Types of Study Considerations

- Trial population not representative of broader patient population that receives therapy
- Establishing effectiveness in subgroups of the general population, especially those excluded from conventional RCTs
- Administration of an intervention (e.g., differences in routine practice vs. RCT)
- Real-world adherence
- Acceptability for patients in real practice
- Evidence gaps for comparisons with routine standard of care
- Position of new treatments within current treatment paradigms
- RCT comparators that differ from routine standard of care
- RCT outcomes not considered to be the most relevant measures of effectiveness (e.g., surrogate endpoints used and data on clinically relevant endpoints desired)
- RCT treatment pathway is not representative of usual practice
- RCT sites are not representative of usual care settings

where the primary aim is to understand the effectiveness of a drug or other health intervention, and to empower patients, providers, and organizations to be able to make informed evidence-based choices to improve patient health and/or satisfaction. Depending on the research question, some pragmatic trials, especially large simple trials, may include placebo arms and, where multiple interventions are to be tested in a single trial population, also factorial randomization schemes. Evidence from pragmatic trials is not limited to a post-approval context (see Salford Lung Studies),⁹ though it is a strong research design for comparative effectiveness research where approved treatments already exist, as well as when the

One aim of trial design is to streamline study procedures, reduce complexity, and minimize the burden on participants, their clinical caregivers, and study sites.

real-life situation (patients, providers, care systems) is expected to influence the treatment effect. Interactions between elements of actual care, patient and disease characteristics, and health system policies may result in observed differences in effectiveness in a pragmatic trial versus efficacy demonstrations under a specific set of (often more ideal) conditions (Figure 3), the so-called efficacy-effectiveness gap.¹⁰ It is important to anticipate any impacts on effectiveness that may arise and to explore these issues to increase understanding of drivers of effectiveness that may be amenable to modification to improve patient care.

Focus on Patient-Centered Outcomes

Clinically Relevant Endpoints

One aim of trial design is to streamline study procedures, reduce complexity, and minimize the burden on participants, their clinical caregivers, and study sites. To answer the primary research question, pragmatic trials focus data collection activities on a limited number of variables that are both clinically meaningful and important to patients. Such trials often make use of composite endpoints comprised of a collection of clinical events that presumably share an underlying biological basis. Composite endpoints can be particularly useful when the disease being studied has a variety of clinical consequences, and can be used to either reduce the sample size or increase the sensitivity of the trial to detect moderate levels of effectiveness (e.g. JUPITER trial,¹¹ Physician’s Health Study,¹² and Women’s Health Study¹³).

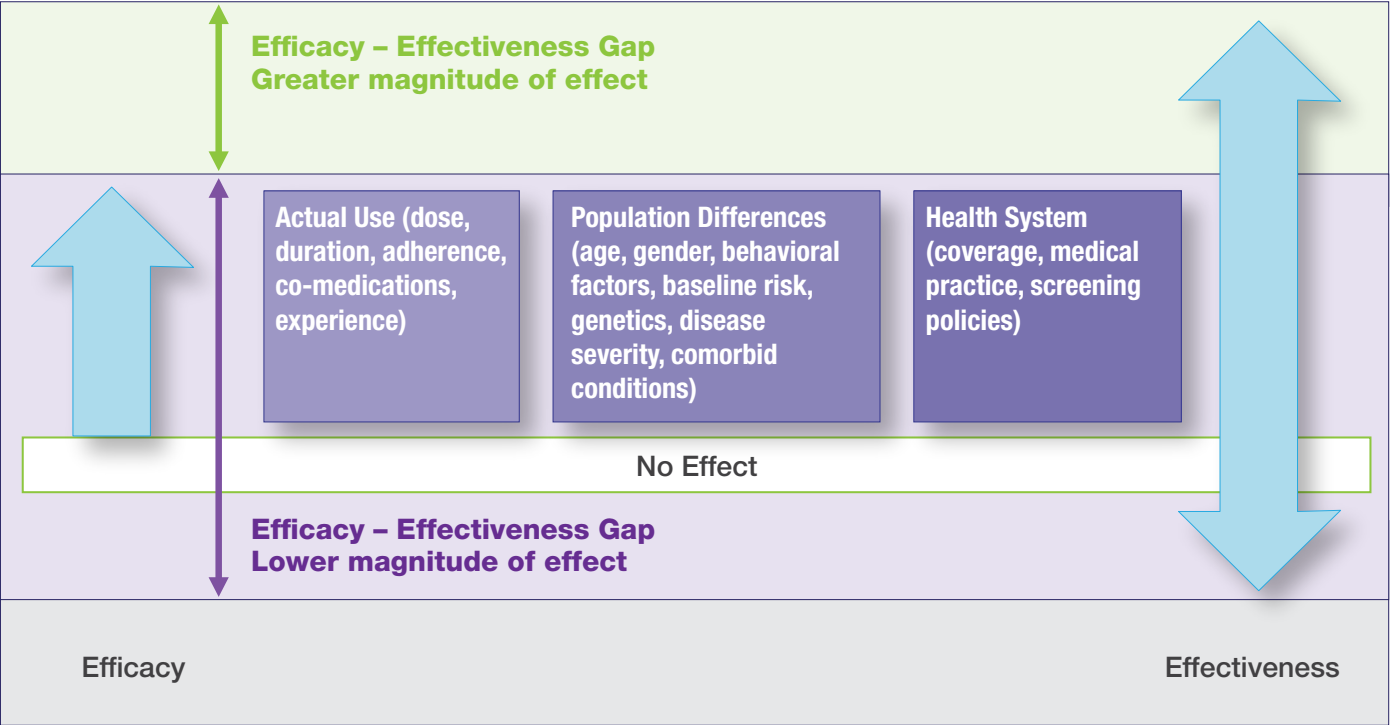
Patient-Reported Outcomes

Patient-reported outcomes are increasingly incorporated into explanatory trials, and their place in pragmatic trials is central. It is important to give thoughtful attention to inclusion of patient outcomes including securing the necessary expertise to assess existing patient-reported outcomes (PROs), the potential need for development of novel PROs, and the collection and integration of patient-centric information across various dimensions of the patient experience.

Ambient Physiological Measures

A burgeoning selection of patient/physiological monitoring devices with the potential to provide real-time data on important indicators is an emerging area of innovation with likely applications in the pragmatic trial setting. When there

Figure 3. The Efficacy – Effectiveness Gap



is no major difference in clinical outcomes, differences in symptoms, common adverse events, and quality of life are critically important to patients and caregivers. For certain indications physiological monitoring may be highly predictive of a clinically relevant endpoint and real-time collection of symptom scores is another potential application. Regulatory guidance on use of mobile apps for reporting of adverse drug reactions (ADRs) and use of social media is under development.

Safety

Ensuring the safety of medicines or other health interventions is a fundamental requirement for continued market authorization, with increasingly active and data-driven scrutiny in the post-approval period (e.g., the FDA's SENTINEL system). Whereas well tested procedures for assessing the safety risk in new medicines exist and are required for regulatory review, approval, and post-approval monitoring, the limitations of pivotal RCTs in terms of restrictions in patient populations studied, ideal conditions versus actual use, and monitoring, etc., and passive pharmacovigilance highlight the importance of a transition to active real-world safety (safety epidemiology) assessments post-approval. These can be done through observational epidemiology techniques using available datasets such as in the SENTINEL model, and there may also be a role for the pragmatic trial in certain cases to actively investigate potential safety issues (e.g., in a comparative safety trial) while overcoming potential bias that may arise in database studies, such as prognostic incomparability between patient groups. In the more

Incorporation of pragmatic trial characteristics may lead to operational challenges that differ from those typically encountered in explanatory trials.

pragmatic setting, it can be more challenging to study and understand drug safety when relevant data were not systematically collected as part of the original data collection process. For trials primarily designed for effectiveness, the FDA's guidance document "Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Postapproval Clinical Investigations" gives clear guidance to sponsors that it may be appropriate to adopt a selective approach to safety data collection when the safety profile of the drug for common, non-serious adverse events has been established.¹⁴ This is most likely to be the case for investigations of new indications for approved drugs, post-marketing commitments, large late-stage pre- or post-marketing outcome trials (such as most pragmatic trials), and post-approval investigations on a different population, etc. Three types of selective safety data collection are outlined, including: 1) no collection of certain safety data; 2) less frequent collection of certain safety data; and, 3) collection of certain safety data from

only a fraction (e.g., 10%) of the total trial enrollment.¹⁴ However, as requirements remain more restrictive in some countries, sponsors of a multinational trial would need to conform to the most restrictive regulatory regime. Indeed, the guidance speaks directly to the benefits of selective safety monitoring to facilitate the conduct of large trials. As always, a sponsor should consult with the FDA to determine whether selective safety data collection would be appropriate, and, if so, develop its plan for implementation.

Operational Aspects/Challenges

Incorporation of pragmatic trial characteristics may lead to operational challenges that differ from those typically encountered in explanatory trials. Nearly all trials will impact usual care in some way, and depending on the design, upfront engagement with leadership of the healthcare systems may be needed to enable investment of managerial time and systems support to minimize the impact of a trial on frontline providers. (Notable exceptions include some LSTs such as the Physicians' Health Study where participants are contacted and enrolled directly, outside of their healthcare system, and then followed-up using a combination of self-reported information, medical record review, and linkages to claims data.) Getting support from health system leaders and frontline providers can be facilitated if the trial is designed to test a question of interest that will help inform clinical decision-making. Since they are conducted in more real-world settings, cultural differences among the variety of disparate teams from different professional cultures (academia, clinical, pharmaceutical industry, operations, etc.) may require proactive mechanisms to define ways of working, accountabilities, etc.

To garner a representative sample that better approximates the real world, a pragmatic trial needs to appeal to a broad range of site participants. This involves a balanced cross section of academic centers and community-based sites. While the former may be well versed in the rigorous standards of clinical research, the latter may be dabbling in research for the very first time. A well-thought-out study training curriculum is highly advisable, in addition to basic clinical training such as Good Clinical Practice (GCP) and informed consent (ICF) procedures. This will ensure that even the least experienced participant is astute and knowledgeable enough to provide quality data and pass regulatory inspection.

The observational nature of a pragmatic trial means the pace of enrollment cannot be wholly driven by the protocol. Despite randomization, a subset of study participants will typically be prescribed the sponsor product. Enrollment, therefore, cannot be encouraged to the extent that it is perceived as inducement. As such, expectations around study milestones and publication planning need to be kept relatively flexible, with contingencies in place should enrollment prove to be more languid than desired.

Examples

Case Study 1: Label Change¹⁵⁻¹⁷

Study Overview: While debatable where the JUPITER trial (safety and effectiveness of rosuvastatin vs. placebo) lies on the exploratory-pragmatic spectrum, several pragmatic design elements led the FDA to grant a new indication for this cholesterol lowering medication.

Pragmatic Design Elements:

- **Eligibility:** diverse, representative patient population (~18,000 enrolled across 26 countries)
- **Primary Endpoint:** composite measure of time to first occurrence of cardiovascular events – actionable, patient-centered, and relevant – was important to stakeholders and to health/needs of patients
- **Streamlined Collection of Safety Endpoints:** Studying a large group of patients led to a surprising safety finding – an increase in the number of individuals receiving rosuvastatin who developed diabetes. Because statins are so widely used, there was a heightened public awareness around this finding.

Case Study 2: “Site-Less” Clinical Trial¹⁸

Study Overview: VITAL Study investigates the correlation between daily supplement intake and risk reduction for developing cancer, heart disease, or stroke in 20,000 individuals with no prior history of these conditions

Pragmatic Design Elements:

- **Eligibility/Recruitment:** broadly represented patient population (20,000 ethnically diverse men and women) selected on basis of age not risk factors (e.g., diabetes)
- **Setting:** a true representation of usual care setting; study-site free approach
- **Data Collection:** annual patient completed questionnaire to assess treatment compliance, use of non-study drugs, occurrence of endpoints, cancer and vascular risk factors

This study represents a cost-effective option to study marketed, low-risk interventions in a real-world setting. Benefits of this trial design include reduced costs and time, and enhanced patient adherence to protocol. Through this pragmatic trial, the opportunity exists to create a platform of integrated, ancillary studies to generate a wealth of observational real-world data.

Case Study 3. Pre-Approval Pragmatic Trial⁹

Study Overview: The Salford Lung Studies (SLS) evaluated the benefit-risk profile of a combination medication for COPD and asthma. The SLS represent the first pre-approval pragmatic trials. The intent was to maintain the scientific rigor of a traditional RCT while reflecting everyday clinical practice to the best possible extent. The studies were designed to include patients who often would have been excluded from a traditional RCT.

Pragmatic Design Elements:

- **Eligibility:** Minimal exclusion criteria; trial population was more realistic of everyday practice and was representative of a much broader population
- **Setting:** minimal disruption to everyday clinical care; patient experience as normal as possible
- **Outcome Measures:** endpoints collected were relevant to patients and healthcare decision makers; treatment was compared with ‘usual care’

Challenges included the need for ongoing training and support for investigators with minimal prior research experience and the variable quality of EHR data. This pre-approval pragmatic trial realized the opportunities associated with a digitally enhanced RCT in integrated, real-time data from a variety of sources, complementing existing data provided by the conventional RCT and generated findings that are generalizable beyond the Salford general practitioners.

Overall Takeaway: Demonstrated value of an intervention in the real-world can be generated earlier in the product development cycle by means of a pragmatic trial design.

Site and patient engagement is another key challenge with a pragmatic trial. From the site's perspective, given the standard of care treatment, study remunerations are more modest compared to explanatory studies. Also, pragmatic trials are unlikely to involve novel therapies, so may be less motivating from an innovation perspective. From the patient's perspective, active product is typically not study-provided, which is one of the incentives missing compared to explanatory studies. Furthermore, treatment randomization eliminates a patient and his/her physician's control over the treatment of choice. A patient may be randomized to a treatment he/she prefers less and incur a higher insurance copay. The latter can be mitigated by employing copay cards to equalize out-of-pocket expenses between treatment arms.

The most naturalistic pragmatic trials typically involve one or more supplemental data sources such as administrative claims databases or electronic medical records.

The most naturalistic pragmatic trials typically involve one or more supplemental data sources such as administrative claims databases or electronic medical records. Incorporating these data sources minimizes the likelihood of the Hawthorne effect, a phenomenon where patients (or physicians) change their behavior due to their awareness of being observed. By utilizing external data, prospective data collection can be minimized and thereby reduce the likelihood of this effect. A key challenge with external datasets is integration complexity. This can be relatively straightforward such as harmonizing field names between data sources to something more complex such as data imputation and adjusting for time lag.

Technology / Infrastructure

Existing clinical data collection platforms present opportunities to both enable and enhance patient enrollment in pragmatic trials and minimize data-collection needs. In the U.S., the NIH's Health Care Systems Research Collaboratory (<https://www.nihcollaboratory.org>) and the Patient-Centered Outcomes Research Institute's National Patient-Centered Clinical Research Network (<http://www.pcornet.org>) have undertaken large-scale efforts to empower such opportunities. These efforts will strengthen research capabilities by providing infrastructures that enable healthcare systems to collaborate through shared data, resources, and best practices while safeguarding patient privacy and security.

Discussion

Through the combined individual and collaborative efforts of diverse stakeholders, the stars are aligning for wider adoption of pragmatic approaches to trial design, and not necessarily limited to the post-approval setting. A core strength of the pragmatic trial is the enhancement of external validity and ability to inform clinical decision making. Pragmatic trials should be considered to fill evidence gaps for medicines with known benefit/risk profiles to inform the clinical relevance of new medicines to patients, providers, regulators, and payers. Most traditional RCTs focus on the safety and efficacy of investigational drugs and/or devices and, to meet these goals, enroll a highly selected patient population that is often not representative of the target population and are highly controlled in ways that depart from usual care. Pragmatic approaches apply the methodological advantage of randomization to a variety of study design and operational choices to increase generalizability and reduce as much as possible the burden the study imposes on patients and their doctors. Evidence derived from these approaches has great potential to help improve patient care through understanding the real-world effectiveness and safety of drugs and devices, which aids clinical decision making in a number of possible areas, including, for example, appropriate patient selection (comorbid diseases and therapies, disease severity, etc.), timing of therapy, duration of therapy, comparative effectiveness (e.g., electronic health records [EHR] versus standard of care), and others. Such information adds to available efficacy and safety to better inform the clinical relevance of new drugs and devices to patients, providers, regulators, and payers.

To fully realize the value that can be added through more widespread conduct of pragmatic trials, the field must realize a paradigm shift to incorporate data and operational platforms that can capitalize on data capture through EHRs, registries, PROs, etc., and enrollment infrastructures within integrated health systems. Moving forward, more pragmatic elements will begin to be introduced during the formulation of the clinical development plan. Relevant stakeholders must address challenges to internal validity and analysis of subgroups, treatment changes and multiple comparators, and operational aspects. Important questions that still pose challenges include development and adoption of novel, more streamlined approaches for ethical review, institutional requirements, consent and involvement of patients without putting research participants at risk, or creating the perception of increased risk, as well as both efficient and precise endpoint ascertainment and safety monitoring. □

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Resources for the Design and Conduct of Pragmatic Trials

Refinements in concept and consensus building to incorporate pragmatism in randomized trials have accelerated in recent years. Some useful resources are listed below.

PRagmatic EXplanatory Continuum Indicator Summary (PRECIS-2) offers a framework to help understand and visually represent where trials fall on the pragmatic/explanatory RCT spectrum across nine domains using a graphical representation.^a PRECIS-2 guides decision making on the design of trial domains and enables trialists to think about how applicable trial results will be in the real world, and how trial design choices determine the applicability of a trial (e.g., the ability for a trial result to be applied or used in a particular situation).^b

Eligibility - to what extent are the participants in the trial similar to those that would receive the intervention as part of usual care?

Recruitment - how much extra effort is made to recruit participants over and above what would be used in the usual setting?

Setting - how different is the setting of the trial and the usual care setting?

Organisation - how different are the resources, provider expertise, and the organisation of care delivery in the intervention arm vs. those available in usual care?

Flexibility (Delivery) - how different is the flexibility in how the intervention is delivered vs. usual care?

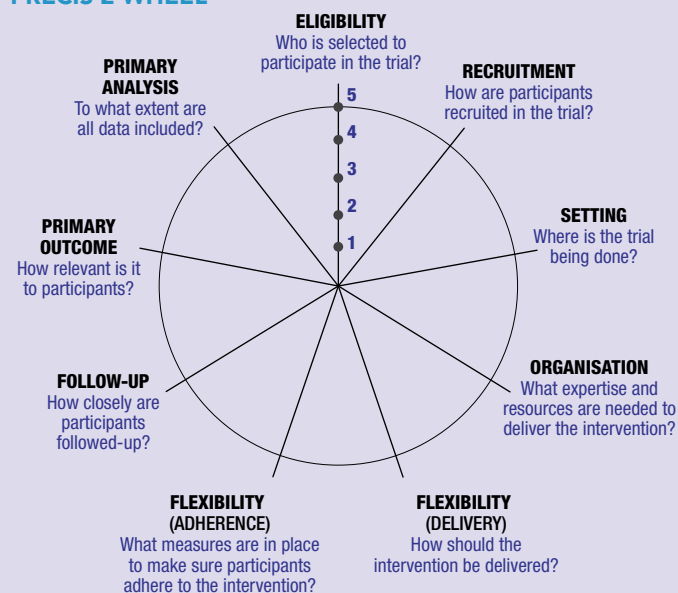
Flexibility (Adherence) - how different is the flexibility in how participants must adhere to the intervention vs. usual care?

Follow-up - how different is the intensity of measurement and follow-up of participants in the trial vs. usual care?

Primary Outcome - to what extent is the trial's primary outcome relevant to participants?

Primary Analysis - to what extent are all data included in the analysis of the primary outcome?

PRECIS-2 WHEEL



NIH Collaboratory Living Textbook on Pragmatic Trials is a virtual home for knowledge about pragmatic clinical trials using health systems, acting as a living resource to guide various stakeholders with an interest in pragmatic clinical trials via a reflection of expert consensus regarding special considerations, standard approaches, and best practices in the design, conduct, and reporting of pragmatic clinical trials (PCTs).^c



Center for Medical Technology Policy Effectiveness Guidance Document, Pragmatic Phase 3 Pharmaceutical Trials: Recommendations for the Design of Clinical Trials that are More Informative for Patients, Clinicians, and Payers^d guides the implementation of pragmatic study designs by providing recommendations for incorporating pragmatism into Phase III clinical trials, while simultaneously meeting regulatory requirements of the FDA. Recommendations focus on the broad topic areas of:

- Enhancing stakeholder engagement in study design
- Aspects of trial design
- Other operational, analytical, and ethical aspects of using pragmatic designs for regulatory approval trials

A concluding output from this guidance indicates that any incremental steps taken to improve the pragmatic nature of trial design by "improving the generalizability of the patient population, selecting active comparators and selecting consistently measured, clinically-relevant outcomes, can markedly improve the utility of information obtained from clinical studies designed for regulatory approval."^d

The **PragMagic** tool, a recently available tool developed by the GetReal consortium of the Innovative Medicines Initiative, builds on prior work, including PRECIS-2, and uses an interactive game-like setting to aid understanding of how various pragmatic design choices impact operational feasibility, study validity and generalizability, and acceptability to patients, prescribers, regulators, health technology assessment bodies, and ethical considerations.^e

The **GetReal consortium of the Innovative Medicines Initiative** has carried out literature reviews and extensive interviews with stakeholders leading to:

- An eight-article series on pragmatic trials published in the *Journal of Clinical Epidemiology* focused on specific design choices^{f-i}
- RWE Navigator, a web-based information hub to aid and understand study design choices by clarifying the issues and finding purpose-appropriate RWE options
- A special 12-article issue of *Clinical Trials* focused on ethical and regulatory issues in pragmatic trials^m

Institute of Medicine workshop output: Large Simple Trials and Knowledge Generation in a Learning Health System: Workshop Summary.ⁿ



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21ST Century Cures Act

Innovation, Breakthroughs, and Research in Under-Represented Populations

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Background

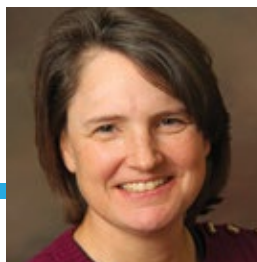
On December 13, 2016, the 21ST Century Cures Act (H.R. 34) (the Act) was signed into law by President Obama.¹ Provisions in the Act were negotiated between the House and the Senate over a two-year period. The first version of the Act, the “21ST Century Cures Initiative,” was introduced by the Energy and Commerce Committee in April 2014.² The Act is a bipartisan agreement to fund and accelerate cancer research and overall medical product discovery, development, and delivery (Division A, the 21ST Century Cures Act); to help families in mental health crisis (Division B); and, to increase the choice, access, and quality in healthcare for Americans (Division C).

The 21ST Century Cures Act Division A

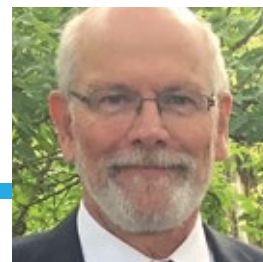
Division A of the 21ST Century Cures Act provides funding for innovation projects and state responses to opioid abuse, precision medicine, and new drug discovery and development initiatives, and the overhaul of healthcare product regulations by the U.S. Food and Drug Administration (FDA). The regulatory affairs sections

support product research and innovation, encourage acceptance of patient and real-world experience data, and call for streamlined marketing approvals for innovative medicines and devices, as well as for supporting the participation of certain less-represented population groups in clinical investigations.

Division A is divided into subparts to address: a) funding for various program initiatives for research and innovation; b) the overhaul of medical product regulations; and, c) the need for mental health initiatives. The funding details for various programs and mental health initiatives are not subjects of this article. Of greater interest from the regulatory and market access perspective are the regulatory-related provisions to allow the inclusion of patient experience and real-world data in marketing applications; the inclusion of pregnant and lactating women, as well as children, in clinical trials; the acceleration of medicinal product development and approval by implementation of expedited pathways; and, the creation of one or more intercenter institutes within the FDA to develop and coordinate activities on major disease areas.



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Initiatives Specific to Women and Pediatric Patients

A long-standing problem area in clinical trials has been restrictions on the enrollment of pregnant and lactating women, children, and the elderly due to their respective vulnerability and special protections in place for these study populations. The enrollment of women and particularly those who are pregnant or lactating has historically been lacking or inconsistent.³⁻⁶ Most clinical trials require use of contraception by women of childbearing age, therefore knowledge gaps as to treatment benefits for this “scientifically complex” population remain.³ The “Task Force on Research Specific to Pregnant Women and Lactating Women,” established by the National Institute of Child Health and Human Development, has scheduled several meetings throughout 2017 and into 2018 to identify and develop guidance to address gaps in knowledge required for the development of safe and effective medicines for pregnant and lactating women.⁷

The enrollment of women and particularly those who are pregnant or lactating has historically been lacking or inconsistent.³⁻⁶

Clinical research in children is necessary to assure safety and efficacy of any drug under development because of physiologic and metabolic differences to the adult population for which most drugs are approved. Additional safeguards for children to be involved in research studies are necessary, which make clinical trial designs more complex. Recognizing the difficulties of conducting research in the pediatric population, Section 2072 of the Act mandates the establishment of a global pediatric clinical study network to provide grants, contracts, or cooperative agreements to support new and early stage investigators.¹ The participation of international authorities outside of the United States will be actively supported and maintained in the operating network.

Development of Regenerative Medicines

The opinion that the FDA does not approve new innovative medicines fast enough and prevents patient access to these medicines is addressed in the Act through the implementation of a host of provisions for accelerated approval pathways for regenerative advanced therapies as well as innovative devices. Most notably, the Regenerative Medicine Advanced Therapy (RMAT) Designation, which was originally labeled as “Regenerative Advanced Therapy or RAT,” introduced in Section 3033 of the Act, builds on the existing four expedited development and review programs offered by the FDA.¹ A few RMAT designations have already been granted (*Table 1*).

The new RMAT designation provides the FDA with a program for expanding expedited review pathways for regenerative medicines without lowering safety or effectiveness standards. For example, a drug would be

eligible for this designation if the drug is a regenerative medicine (cell therapy, therapeutic tissue engineered products, human cell and tissue products, and combination products except those solely regulated under PHS 361) intended to treat, modify, reverse, or cure a life-threatening disease/condition and preliminary clinical evidence indicates that it would meet an unmet medical need.⁸ A drug designated as RMAT may be eligible for priority review and accelerated approval based on surrogate or intermediate endpoints likely to predict long-term benefit or on data from a meaningful number of clinical sites. Notably, products with RMAT designation can fulfill post-marketing requirements through channels additional to clinical trials, such as patient registries, real-world experience (e.g., electronic health records), collection of large confirmatory data sets, or post-approval monitoring data.

There has been controversy around the RMAT designation. An article in *Wired* states that under the 21ST Century Cures Act, “FDA would have the authority to grant accelerated approval for regenerative medicines, skipping straight from animal models and safety trials, over efficacy testing in humans, to post-marketing review.”⁹ It further states that it provides a direct path for acceptance of regenerative medicines by stem cell clinics – dubbed the “medicine’s wild west” for an “inject and see” era.⁹ Husten calls the provision repulsive.¹⁰ Accelerated approval would only be granted based on surrogate or intermediate endpoints likely to predict a long-term clinical benefit or on data obtained from a meaningful number of sites, which is quite different from what the two critical articles suggest. Also, standards for approval of other expedited programs would remain.¹¹

On the other hand, the REGROW Act¹² introduced by U.S. Sen. Mark Kirk early in 2016 would have allowed conditional approval of cell and tissue therapies based on preliminary clinical evidence of safety with reasonable expectation of efficacy, without the initiation of Phase III studies. Unlike the REGROW Act, the 21ST Century Cures Act does not eliminate the need for Phase III studies but allows reliance on surrogate endpoints and other intermediate endpoints.¹³

Unlike the REGROW Act, the 21ST Century Cures Act does not eliminate the need for Phase III studies but allows reliance on surrogate endpoints and other intermediate endpoints.¹³

Currently, seven companies have publicly announced that their product received RMAT designation. FDA does not publish this information and it is at the discretion of the company to publish the assignment of the designation.

The 21ST Century Cures Act mandates that the FDA track the applications for RMAT designation, the number of

Table 1: RMAT Designations under the 21ST Century Cures Act

Company	Product	Description	Indication	Date
Humacyte ¹⁴	Humacyl®	Human acellular vessels	Kidney failure (vascular access for hemodialysis)	20 March 2017
Enzyvant ¹⁵	RVT-802	Apply allogeneic thymus tissue to restore some immune function	DiGeorge syndrome	17 April 2017
jCyte ¹⁶	jCell	Human retinal progenitor cells release neurotrophins to potentially rescue diseased retinal cells	Developmental retinitis pigmentosa	2 May 2017
Vericel ¹⁷	Ixmyelocel-T	Autologous multicellular therapy of mesenchymal stromal cells and macrophages to repair damaged tissue	Serious cardiovascular disease	10 May 2017
Mallinckrodt ¹⁸	Stratagraft®	Autologous skin tissue	Complex skin defects due to thermal burns	18 July 2017
Kiadis Pharma ¹⁹	ATIR101™	Adjunctive immunotherapeutic of donor lymphocytes	Blood cancers	20 September 2017
Asterias Biotherapeutics ²⁰	AST-OPC1	Oligodendrocyte progenitor population derived from embryonic human stem cells	Spinal cord injury	2 October 2017

designations issued, and the ultimate disposition of the products involved per approval pathway, approvals, withdrawals, and authorization denials. The FDA is required to submit a report to Congress by March 1 of each calendar year of the applications and outcomes for the prior fiscal year. Furthermore, the FDA is required to develop guidance clarifying how devices used in the recovery, isolation, and delivery of regenerative advanced therapies will be evaluated (Section 3034).¹

The 21ST Century Cures Act also mandates the development and implementation of a set of standards and consensus criteria to support the development and evaluation of regenerative therapy medicinal products or devices (Class III) used with a regenerative therapy product to ensure regulatory predictability. In August 2017, the FDA issued a call for proposals to complete this task and requires the interaction of a mixed group of stakeholders, with public involvement, to develop the standards, set criteria, and provide a process for implementation and oversight. (Read more in “Leveraging Real-World Evidence for Regenerative Medicine and Advanced Therapy Success Beyond the Regulator” in this issue.)

Medical Device Regulatory Changes

The 21ST Century Cures Act contains several provisions that support faster access to medical devices. Most notably Section 3051, inserting Section 515C into the FD&C Act (21 U.S.C. 351 et seq.), implements the new Breakthrough Device Designation to expedite the development of devices that represent breakthrough technology. Although, the Breakthrough Device Designation is like the 2015 Expanded Access Program (EAP) for devices,²¹ there are some differences, for example:

- 510(k) devices are eligible for the Breakthrough Device Designation, whereas only devices requiring premarket approval or de novo applications were accepted for the EAP; and,
- The Data Development Plan is now optional rather than mandatory.

The designation can be obtained if the device:

- a) provides for more effective treatment or diagnosis of life-threatening or irreversibly debilitating disease, and
- b) 1. represents breakthrough technology,
2. no approved or cleared alternative exists,
3. shows significant advantage over existing alternatives, or
4. availability is in the best interest of patients.

Advantages of receiving the designation include assignment of a dedicated FDA staff team, interactive and timely communication with the FDA during the development and review process, agreement of a data development plan, ensuring clinical trial design is as efficient and flexible as practicable, and agreement on clinical protocols and priority review for market approval. This new program replaces the priority review previously noted in FD&C Act Section 515(d)(5). The FDA is expected to issue guidance for sponsors within a year. To date, two companies publicized receiving the Breakthrough Device Designation.

NeoTherma Oncology announced in April that its Vectron Thermal Treatment (TTx) system for treatment of pancreatic cancer was designated a Breakthrough Device. The Vectron

TTx system integrates electromagnetic field physics with thermographic imaging and computational imaging to modestly raise the temperature in the tumor environment. This adjuvant treatment was shown to significantly increase the effectiveness of radio-, chemo-, and immunotherapies.²² Also in April 2017, N8 Medical, LLC received the breakthrough designation for their CeraShield Endotracheal Tubes. The endotracheal tubes, coated with a proprietary ceragenin compound, prevent bacterial and fungal growth while a patient is intubated for mechanical ventilation.²³

Additional provisions of the 21ST Century Cures Act include Section 3052 that amends the Food Drug and Cosmetic Act to extend the Humanitarian Device Exemption from a previous maximum of 4,000 to the new maximum of 8,000 patients. More flexibility for the recognition of standards is introduced by Section 3053. Any person can submit the request for recognition of a standard established by a national or international standards organization. The Secretary will determine if the standard is recognized in part, full, or not at all and inform the requestor. The Act also provides for the establishment of new requirements for medical device classification panels, Clinical Laboratory Improvement Amendments (CLIA) waiver improvements, and a requirement that FDA staff are to determine the least burdensome pathway to demonstrate reasonable assurance of safety and effectiveness during review of 510(k) premarket notification and premarket approval applications.

Conclusion

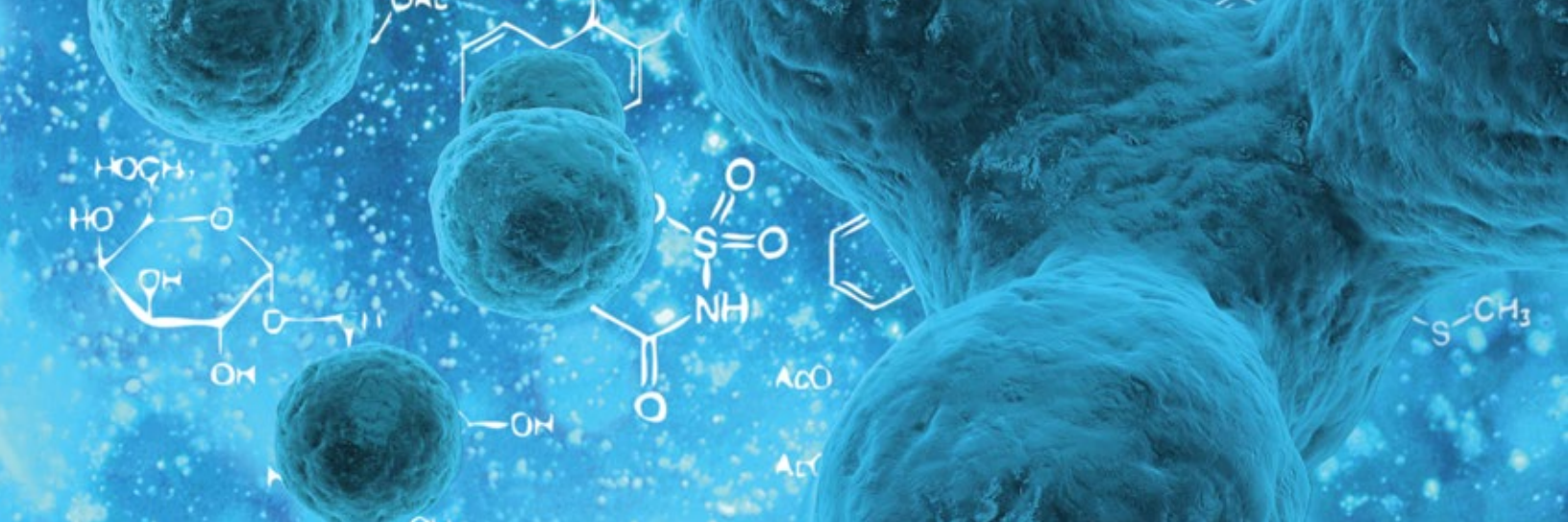
The 21ST Century Cures Act brings about many regulatory changes. The implementation, and particularly the timeframe to achieve this, is very ambitious. The implementation of tools to allow for more efficient drug approval, e.g., regenerative medicine advanced therapy designation (Section 3033), breakthrough devices (Section 3051), and summary level review (Section 3031) have been met with criticism, citing lower standards for approval and the potential for ineffective or unsafe drugs or devices entering the U.S. market. However, it is important to consider the legislative text of the 21ST Century Cures Act that includes provisions to safeguard the current FDA approval standards. On the other hand, provisions such as the RMAT designation and the breakthrough device designation have been met with great enthusiasm from industry. Several applications have been approved since the Act was signed into law. Since the number of applications currently is not public information, the reports required from FDA on a yearly basis by March 1 for the preceding fiscal year will provide a better picture. Some of the task forces mandated by the Act have been formed already, but to see results from their work will take some time. □

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Leveraging Real-World Evidence for Regenerative Medicine and Advanced Therapy Success Beyond the Regulator

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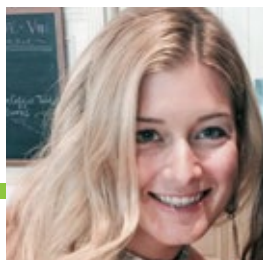
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Regenerative Medicine Therapy – Signs of a Promising Future on Multiple Fronts

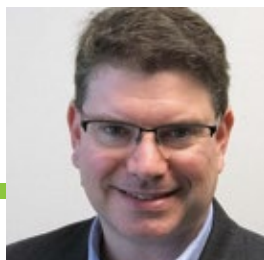
In today's healthcare environment there is a great need for treatments capable of reversing or significantly impacting the progression of and costs associated with serious illnesses. Enter regenerative medicine – treatments with the potential to transform the healthcare landscape by offering transformative, durable and (in some cases)

even potentially curative outcomes targeting many of our highest unmet need scenarios, including life-threatening acute and chronic conditions, injuries, degenerative diseases, genetic disorders, and cancer.

With more than 822 regenerative medicine companies worldwide and 899 clinical trials utilizing specific regenerative medicine/advanced therapy (RM/AT) technology currently underway (half of which are in oncology) as of mid-year 2017,¹ as well as notable strategic alliances including industry and academic partners, future disruption of traditional medicine approaches by regenerative medicine therapies is certain. According to the World Regenerative Medicines Market forecast for 2013–2020, the global market for small molecules and biologics, gene therapy, and cell therapy is expected to grow to \$67.5 billion by 2020 (a more than four-fold increase from \$16.4 billion in 2013).² Regenerative medicine saw venture capital investment nearly quadruple from ~\$200 million in 2010 to ~\$800 million in 2016, signifying a 34% average year-over-year growth rate during that period.³ The strong, consistent investment and market growth in the regenerative medicine space signals a future intensely-competitive landscape where differentiating product value will be key.



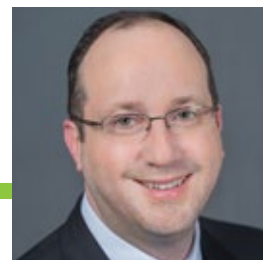
Marissa Mihos



Daryl Spinner



Moirá Ringo



Eric Faulkner

In addition to investment trends and the demand for transformative treatment approaches, recent U.S. Food and Drug Administration (FDA) policy updates are also actively contributing to the advancement of and access to regenerative medicine therapies. In December 2016, the 21ST Century Cures Act was signed into law in the United States. Section 3033 of the legislation establishes an optimized FDA approval pathway for regenerative medicines therapies, encouraging innovation while striking a balance between patient safety and accelerated access to regenerative medicine products. Under this recent legislation, the definition of regenerative medicine has evolved from previous versions towards greater emphasis on product type in combination with unmet medical need.⁴ The Cures Act defines regenerative medicine as: “cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products intended to treat, modify, reverse, or cure a **serious or life threatening disease** with **preliminary clinical evidence** demonstrating the potential to address **unmet needs**” (Figure 1). The value of these treatments is driven by patient benefit which must be transformative and exceed that provided by already available options.

Section 3033 newly defines a Regenerative Medicine Advanced Therapy (RMAT) designation, which may be considered analogous to the previously-established breakthrough therapy designation (See FDASIA Section 202) but is specific to regenerative medicine.⁹ Achieving an RMAT designation extends potential benefits for regenerative medicine sponsors, including an accelerated regulatory path to market.

The Cures Act and RMAT designation signify enhanced recognition of the significant potential patient benefit of regenerative medicine therapies in several chronic or inherited disorders and requires the FDA to account for clinical evidence beyond “traditional” randomized controlled trials (RCTs), including real-world evidence (RWE) approaches that may be integrated into the approval process. This provides both an opportunity and evidentiary hurdle for the industry. On the one hand, it provides greater flexibility for building a value case to support new regenerative therapies, but on the other hand, it may also increase complexity and uncertainty in terms of acceptable evidence to support approval.

While qualifying for RMAT designation might enable more rapid regulatory approval and patient access to regenerative and advanced therapies, sponsors must also contend with a number of access and commercial uncertainties, some of which are unique to regenerative medicine, both in the U.S. and globally (Figure 2). Rapid evolution of regenerative and advanced therapy platforms, patient recruitment hurdles, and compressed timelines for planning a successful product launch, while sufficiently difficult on their own, are only the tip of the iceberg for successful value demonstration for regenerative medicines. There are also significant hurdles associated

Figure 1. Key Terms Defining Regenerative Medicines in the 21ST Century Cures Act

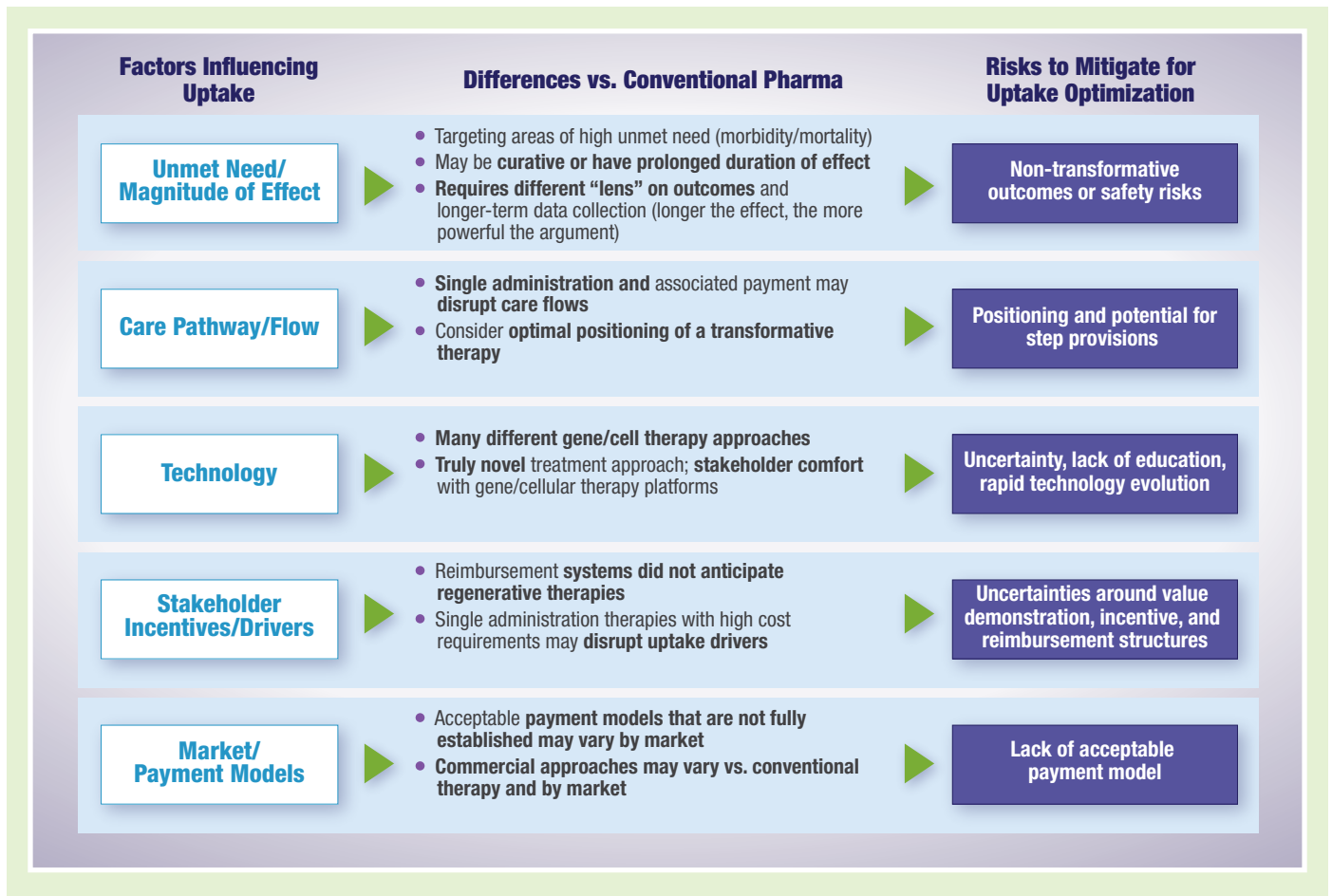
Serious or Life Threatening Disease⁵	Disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible if it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.
Preliminary Clinical Evidence	Preliminary data could be comprised entirely of “traditional” clinical trial data (including early/interim, or non-U.S. data), or may include data from “non-traditional” studies that include adaptive designs, enrichment strategies, crossover, or N-of-1 designs, and/or use of historical controls and other real-world data sources, etc. ⁶⁻⁸
Unmet Need	Condition whose treatment or diagnosis is not addressed adequately by available therapy. An unmet medical need includes an immediate need for a defined population (i.e., to treat a serious condition with no or limited treatment) or a longer-term need for society (e.g., to address the development of resistance to antibacterial drugs). ⁷

with fast-tracking technologies, whose primary value proposition drivers are magnitude and duration of effect, into an HTA and payer environment that was not structured to receive them. Under such a model, faster entry into market may come at the expense of sufficient data to optimize patient access and product pricing. This means that regenerative medicine developers must take a more comprehensive and longer view on value demonstration to balance a regulatory landscape that is shifting to address them against a reimbursement environment that is not yet fully ready for optimal acceptance and uptake of these therapies. Long-term success in a global reimbursement environment with high levels of scrutiny will depend on characterizing value that addresses the impact, duration of effect, and comparative value of regenerative and advanced therapies beyond that associated with standard of care or conventional agents. This article will consider the value of comprehensive and real-world evidence generation for regenerative and advanced therapies beyond the regulator.

Regenerative Medicine and Advanced Therapies Differences vs. Conventional Pharmaceutical Therapies and Core Value Demonstration Opportunities

To mitigate potential challenges and balance early opportunities for regulatory approval against successful market uptake, it is important to understand key differences between innovative regenerative medicine therapies and conventional pharmaceuticals and what risks they represent for technology developers.

Figure 2. Factors Influencing Uptake of Regenerative Medicine Therapies and Differences vs. Conventional Pharmaceuticals



Adapted from Faulkner E and Han D. *Addressing Uncertainty in Regenerative Medicine Value Demonstration: What is Mission Critical vs. Mission Impossible?* (Meeting on the Mesa, Alliance for Regenerative Medicine, La Jolla, CA, October 2016); and, Faulkner E. *What Value Do We Place in a Cure? Implications for Regenerative Medicine Technologies* (Phacilitate Cell and Gene Therapy Meeting 2015, Washington, DC, January 2015).

Benefit

Clinical trials for regenerative medicine therapies are often insufficient to capture the total magnitude of potential benefit to the patient, the payer, and the healthcare system overall. Contributing factors to this hurdle include rapid evolution and variability of early regenerative and advanced therapy platforms; the need to demonstrate longer-term benefits of transformative and potentially curative treatments versus historical trial considerations; and, unknown side effects associated with these truly novel therapies. Use of real-world evidence (RWE) approaches will be critical to establishing the transformative benefit, durability, and safety outside of the pivotal studies needed for regulatory approval. Because many of these therapies may also have higher costs than conventional therapies, manufacturers should also anticipate stakeholder scrutiny to be high and that payers will seek opportunities to limit access to those patient populations and scenarios sufficiently covered in pivotal studies. In regenerative medicine, compared to other therapy areas, RWE studies can help manufacturers effectively and affordably bridge the gap between the need to rapidly gain the market versus the need to paint a broader picture of value that optimizes acceptance, pricing, and patient access potential.

Real-World Evidence is defined in the Cures Act as **“data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than RCTs.”**

Looking to the FDA guidance published on the use of RWE in medical devices and future FDA RWE frameworks for approving follow-on indications labels for drugs mandated by the Cures Act,¹⁰ other sources of evidence could include:

- large simple trials or pragmatic clinical trials
- prospective observational or registry studies
- retrospective database studies
- case reports
- administrative and healthcare claims
- electronic health records
- data obtained as part of a public health investigation or routine public health surveillance
- data gathered through personal devices and health applications

Certain assumptions may be drawn from recent medical device guidance regarding the value and appropriateness of RWE in the regenerative medicine arena.¹¹ If appropriately validated and considered “sufficient,” data from RWE sources have the potential to provide valuable insight into the effectiveness of regenerative medicine therapies in actual clinical scenarios, thus confirming clinical benefit. RWE can also provide answers to research questions (e.g., burden of illness/natural history, comparative treatment landscape, epidemiology and patient subpopulations considerations, market access bridging studies following pivotal trials, and demonstration of long-term effectiveness and safety) not easily addressed in other ways during pre-launch and post-launch periods. Under the RMAT pathway where the regulatory timeline is accelerated, it will be even more critical to consider comprehensive value demonstration strategy for regenerative therapies that “fill in the blanks” not easily covered by short-term pivotal trials. Some EU and other markets may also require longer-term data collection as a condition of early acceptance.

Linking the Evidence Tool Kit to the Most Important Value Demonstration Issues

Because regenerative medicine therapies are often truly novel and will face increased payer and provider scrutiny, one should anticipate additional “asks” and longer-term evidence demonstration periods. In establishing an evidence optimization plan for regenerative and advanced therapies, developers should first consider the unique value and access challenges associated with these therapies (Figure 3).

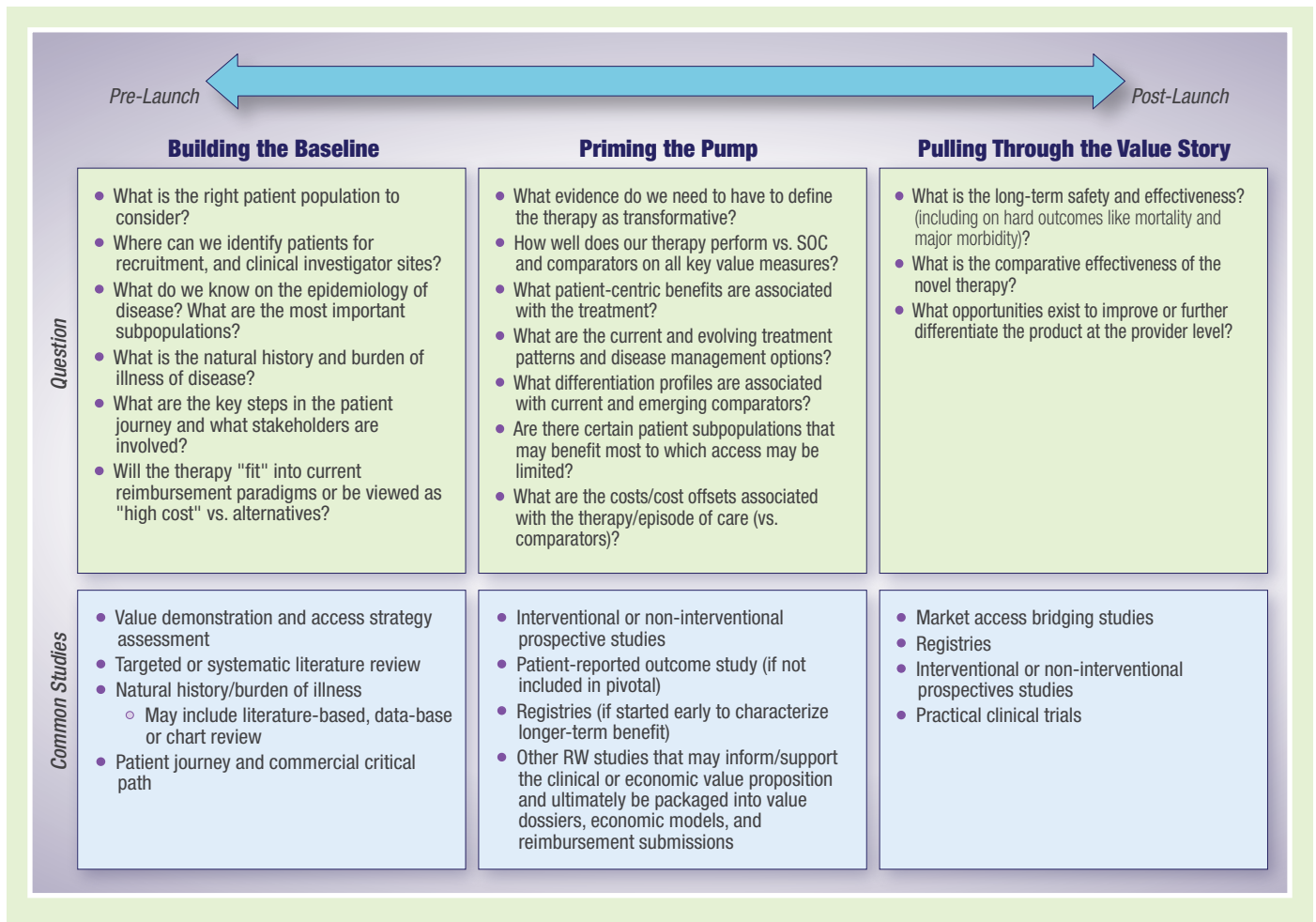
In anticipating value and access challenges for novel regenerative medicine therapies, the importance of an early, proactive, strategic approach to evidence generation and value demonstration is often overlooked. Questions that address specific value and access challenges, as well as some specific to primary clinical development, require targeted research starting well in advance of product launch, and ideally prior to pivotal study protocol finalization and initiation. This research often involves a combination of secondary research of the competitive landscape and sources like clinical guidelines, health technology assessments (HTAs), and coverage policies to understand “what has come before,” patient journey, unmet need, and product positioning, as well as primary research with the range of healthcare stakeholders that will play a role in acceptance and uptake (e.g., providers, hospital administrators, payers, third-party intermediaries). Given common limitations associated with planning clinical studies for novel regenerative medicine treatments (e.g., trial site selection, patient recruitment, blinding, direct comparison and randomization, cross-over design), supplementing traditional study designs with RWE approaches is often the most efficient, flexible, and/or only feasible way to address identified evidence gaps that may limit or preclude market access and commercial optimization.

RWE studies addressing key regenerative medicine questions should be considered as part of early product development activities, beginning as early as Phase I, but most critically before committing to protocols for Phase II/III studies (Figure 4). We refer to three key domain opportunities for leveraging RWE to address development

Figure 3. Core Value and Access Challenges for Regenerative Medicine and Advanced Therapies



Figure 4. Aligning Regenerative Medicine Evidence Questions with RWE Approaches



Adapted from Faulkner E and Han D. Addressing Uncertainty in Regenerative Medicine Value Demonstration: What is Mission Critical vs. Mission Impossible? (Meeting on the Mesa, Alliance for Regenerative Medicine, La Jolla, CA, October 2016.)

challenges as **Building the Baseline**, **Priming the Pump**, and **Pulling Through the Value Story**, which we define above and use to categorize key questions that developers must address. These RWE approaches can be employed to address key questions and potential pitfalls that regenerative medicine developers should plan to avoid. This article does not cover the fourth increasingly critical domain which could be titled **Maintaining Access and Commercial Position**, where stakeholders in many markets (e.g., Australia, Netherlands, Sweden, and the U.S.) are more aggressively conducting periodic assessments of product and product class value and leveraging these assessments to alter coverage positions over time based on available evidence.

Building the Baseline is defining the evidentiary basis with which the novel therapy will need to be compared, how patients progress to the point of need, and the extent of unmet need that could be filled by a novel therapy/intervention.

Priming the Pump is characterizing value by developing both evidence in pivotal studies and the myriad "wrap around" studies that are increasingly essential to

acceptance and uptake. Therapies that encounter major obstacles to reimbursement often fail to recognize and fill the most critical evidence gaps.

Pulling through the Value Story in the context of regenerative and advanced therapies is anticipating the need to demonstrate evidence of long-term effectiveness and safety and level/nature of proof that pivotal outcomes translate into longer-term transformative benefit.

One of the first questions to consider in your evidence generation strategy is: **what's the level of unmet need and what's the potential to demonstrate transformative improvement associated with regenerative medicine use?** Understanding the baseline outcomes associated with standard of care and core competitors will be necessary to characterize how much better the new therapy will be perceived. This is particularly true in rare disease or poorly characterized subpopulation scenarios where the baseline is insufficiently characterized. In addition, consideration should be given to **what types of clinical and economic outcomes would be necessary to demonstrate transformative impact or curative intent?** While not relevant to all regenerative or advanced therapies, those

therapies that **do not** develop their value plan with transformative value in mind but would have particularly high prices (particularly if the therapy is based on a single-administration model) may face significant HTA and payer scrutiny and acceptance risks. Other overarching value demonstrations and commercial questions to explore in developing regenerative and advanced therapies may include:

- What is the **anticipated balance of clinical and economic outcomes gain relative to the cost of entire procedure vs. standard of care (SOC) procedures?** This would help answer the question of whether the new therapy may be “worth it” to adopter stakeholders.
- What are the **clinical and economic implications of the existing standard of care alternatives? What is the extent of unmet need?** This would help address the question of what degree of problem are we solving for.
- Is the **population sufficient to support the product commercially?** In some scenarios, irrespective of the degree of potential outcomes or level of product pricing, the commercial benefits may not be sufficient to pursue or offer the therapy on the marketplace (e.g., some rare diseases and precision/targeted populations). This would address the question of whether the development scenario is viable.

There is no one-size-fits-most approach for regenerative medicines or any therapy, but a few common evidence generation tactics are described in Figure 5.

The regenerative medicine sector continues to gain momentum year after year with a growing and robust clinical pipeline. However, with innovation comes the weight of expectation for these therapies to create new solutions that markedly improve health benefits. Opportunities and challenges within today’s marketplace are summarized in Figure 6.

Lessons Learned: Opportunities to Position Regenerative and Advanced Therapies for Success

In light of the insights and issues addressed here, generating appropriate and reliable evidence throughout the product life cycle plays a vital role in improving the uptake potential of regenerative and advanced therapies. Most of the core evidence development approaches that apply are not new, but the novelty of the technology and unique evidence/reimbursement issues coupled with stakeholder cost concerns guarantees that the level of scrutiny will be high. Figure 7 highlights the key activities that regenerative and advanced therapy developers should consider to anticipate stakeholder and market needs and optimize product acceptance and uptake. Many of these study and value demonstration limitations have been noted for many years in reviews of HTAs and payer decisions where >75% of available HTAs studied noted key flaws in clinical or economic evidence presented to support

reimbursement decision making.^{26, 27} Addressing these key points systematically, many of which involve leveraging real-world evidence to underpin core elements of the product value proposition, can help prepare products for success, including in our high pressure global market environment.

Of these steps, the following, in our experience, are critical to set the therapy up for success.

1. Plan to build a comprehensive and long-term value story

- Think transformative – non-inferior study designs will not support acceptance and pricing of regenerative medicines; insufficiently supported surrogate-measures are more likely to expose the asset to acceptance risks.
- Mind the gaps – given the additional scrutiny expected for regenerative and advanced therapies, it is critical to understand the gaps in the value story and address the most important ones to best position the therapy for success.
- Plan to follow outcomes of every patient at every trial stage that receives treatment to strengthen the magnitude and duration of effect story to minimize undervaluation and market uptake delays and align value story with pricing aspirations.

2. Understand the patient (that will be included in the study) and patient journey

- Payers have been clear for the past 15 years in the regenerative medicine industry that there will be no “faith-based” reimbursement and patient populations not included adequately in the study will not have access to the therapy.
- Clearly define the patient population and subpopulations where differential response is possible (which may also enable a “back-up plan” for the asset).
- Conduct a burden of illness/patient journey study (particularly in rare or niche populations) to help contrast the value of the novel regenerative or advanced therapy.
- Understand and align the value story to decision maker informational needs; for regenerative and advanced therapies this may also include unconventional stakeholders beyond the payer (e.g., hospital administrators, transplant administrators, reinsurance agencies, third-party intermediaries, and even financial officers) who may play a role in the reimbursement and pricing value chain.

3. Establish a foundation for rationale for positioning and pricing; ensure outcomes and value story are clear and meaningful

Figure 5. Illustrative Real-World Evidence Generation Tactics to Address Regenerative and Advanced Therapy Challenges

RWE Study Type	Study Objectives and Challenge Addressed B = Building the Baseline / P = Priming the Pump / V = Pulling Through the Value Story	Opportunities to Address Regenerative Medicine Challenges
Retrospective data analyses (linked or unlinked health chart and/or insurance claims review)	<ul style="list-style-type: none"> • Generate epidemiological, clinical, humanistic, and health economic evidence to support burden of illness/unmet need addressed and value of therapy (B) • Define patient journey, diagnostic criteria, subpopulations, key outcomes, and SOC/comparators (B) • Define current and historical treatment landscape (B) • Identify sites with high volumes of patients, and potential investigators for pivotal studies, observational studies, and registries (P) • Quantify healthcare resources utilized (e.g., office and emergency visits, diagnostic tests, hospitalizations) for patients on regenerative medicine therapies vs. SOC and/or other relevant comparators (P, V) 	<ul style="list-style-type: none"> • Characterize and quantify how the therapy addresses disease burden and fills existing unmet need • Define existing treatments, best placement targeting therapy, and where patients may fall through the cracks • Define your transformative or differentiation story • Identify potential sources of key opinion leaders (KOLs), clinical investigators, sites, and patients for trial recruitment to accelerate study enrollment, maximize retention, and identify opportunities to capture key outcomes for all stakeholders • Establish baseline disease outcomes in SOC and/or comparator-treated control patients (especially when blinding and/or randomization not possible, or patients are rare) • Define the resource use associated with alternatives to help make a case for novel coding/payment levels (as appropriate)
Observational data collection in parallel to pivotal study/ RCT	<ul style="list-style-type: none"> • Data collection in parallel with pivotal studies (e.g., other data from trial sites to benchmark clinical, humanistic, and health economic outcomes for regenerative medicine therapy vs. SOC) (P) 	<ul style="list-style-type: none"> • Anticipate and address subpopulation data effects that may be relevant to HTA and payer authorities, but cannot be included in pivotal studies • Identify and collect patient-centric and/or economic outcomes/ healthcare resource utilization data early for a solid economic comparison in patients treated with the therapy vs. SOC/key comparators to differentiate in the field.
Prospective observational (cohort) studies	<ul style="list-style-type: none"> • Define patient journey, potentially relevant patient subpopulations, and SOC/comparators (B) • Monitor evolving treatment landscape (P) • Tracking safety and effectiveness, before, during, and after treatment (P, V) • Monitor treated patients for potential subpopulations who benefit more from treatment, and opportunities for continued product differentiation (P, V) 	<ul style="list-style-type: none"> • Demonstrate real-world durability of treatment effect, and safety post-launch • Define potential increased benefit of therapy in patient subpopulations to support “back-up” plans and offer flexibility of defining more than one route to market access • Monitor for opportunities to improve product or health benefit/ effectiveness and/or safety in the real-world
Registry studies	<ul style="list-style-type: none"> • Capture and track long-term outcomes, safety/effectiveness required by regulators, continued value demonstration for payers, and alternative payment models (V) • Monitor treated patients for potential subpopulations who benefit more from treatment, and opportunities for continued product differentiation (V) 	<ul style="list-style-type: none"> • Demonstrate real-world durability of treatment effect and safety post-launch to support market access as launch sequence progresses • Demonstrate ongoing product value to support global access through prolonged duration of therapeutic effect and safety measures • Monitor real-world use and treatment patterns for other patient populations/follow-on indications • Satisfy regulator requirement for prolonged and ongoing post-marketing safety data with most transformative therapies • Capture key ongoing outcomes to support alternative pricing models/outcomes-based payment increasingly required for costly, transformative therapies¹¹

- Conduct early market research to ensure value story resonates with key stakeholders.
- Be comprehensive in why outcome measures add value.
- Understand that magnitude and duration of effect are key differentiators for regenerative medicine.

4. Characterize the resources and economic impact associated with the therapy

- Think in terms of episode of care beyond the gene or cell product; this is critical for establishing the cost of

the procedure in scenarios where new reimbursement or payment will be required (particularly in inpatient scenarios).

- Characterize the cost offsets and cost-effectiveness of the therapy to align to market requirements and make a strong case for payer acceptance.

As the industry begins to more heavily invest in regenerative and advanced therapies, having a solid game plan for optimizing value demonstration is the most important foundational element required to support acceptance and uptake. Magnitude and duration of effect, safety, and economic impact were cited as the

Figure 6. Opportunities for RWE to Address Key Challenges Observed in Regenerative Medicine Development and Access, and Illustrative Examples

	Key Pitfalls/ Challenges Observed	Opportunities to Address Challenges using RWE	Illustrative Case Examples
Building the Baseline	<ul style="list-style-type: none"> ● Defining who the target patient is and how they get there, especially in indications with “softer” diagnostic criteria ● Defining BOI, especially in rarer indications and those with uncertain diagnostic criteria 	<ul style="list-style-type: none"> ● Demonstrate regenerative medicine comparative efficacy with complete characterization of pre-treated and SOC-treated patients ● Generate natural history data to establish course of disease ● Demonstrate lack of effective treatment options 	<p>Successes: Tisagenleucel (CAR-T therapy) in acute lymphoblastic leukemia (ALL) used RWE approaches to define natural history and BOI in target patients, keys to measuring value vs. alternative options¹²</p> <p>GSK2696273 in ADA-SCID started data collection early on in clinical development, with 7-year median follow-up demonstrating durable long-term therapeutic effect (92%) against established baseline¹²⁻¹⁷</p>
Priming the Pump	<ul style="list-style-type: none"> ● Identifying where to find sufficient target patients to reach trial recruitment goals and adequate powering ● Rapidly recruiting target patients for trial enrollment 	<ul style="list-style-type: none"> ● Retrospective data analysis to identify relevant subgroups 	<p>Challenges: Ixmyelocel-T in critical limb ischemia faced difficulty defining target patients contributing to slow pivotal trial recruitment, insufficient powering to meet primary endpoint, and only met secondary/surrogate endpoints^{18,19}</p>
Pulling Through the Value Story	<ul style="list-style-type: none"> ● Avoiding evidentiary uncertainty in demonstrating “transformative” product value ● Adequately capturing critical measures of value to align with anticipated product pricing 	<ul style="list-style-type: none"> ● Characterize implications of surrogate endpoints to help establish SOC baseline ● Run indirect treatment comparisons alongside pivotal studies ● Anticipate need for retrospective analyses of trial data to identify patient subpopulations ● Real-world, post-market, follow-up plan for safety and effectiveness coupled with a risk sharing strategy to help enable uptake ● Natural history data to establish course of disease 	<p>Successes: Tisagenleucel (CAR-T therapy) single-arm pivotal study in ALL leveraged RWE approaches to demonstrate transformative benefit vs. most-relevant comparator</p> <p>Challenges: Talimogene laherparevec in unresectable metastatic melanoma did not include sufficient direct or indirect comparisons to the most-relevant comparators and patients with differing BRAF status to demonstrate added benefit in Germany, which may have been addressed alongside the pivotal study²⁰</p> <p>Alipogene tiparvovec in lipoprotein lipase deficiency (LPLD), moderate efficacy based on surrogate endpoints (blood triglycerides/chylomicron levels), unclear value relative to price given variable patient response, and non-sustained effect beyond 6-12 months²¹</p> <p>Sipuleucel-T in metastatic, hormone-refractory prostate cancer showed 4 months improvement in OS but not PFS, confounding true benefit in relation to commercial strategy; early retrospective subpopulation analysis may have uncovered greater benefit in certain patient types to hone value story at launch^{22,23}</p>

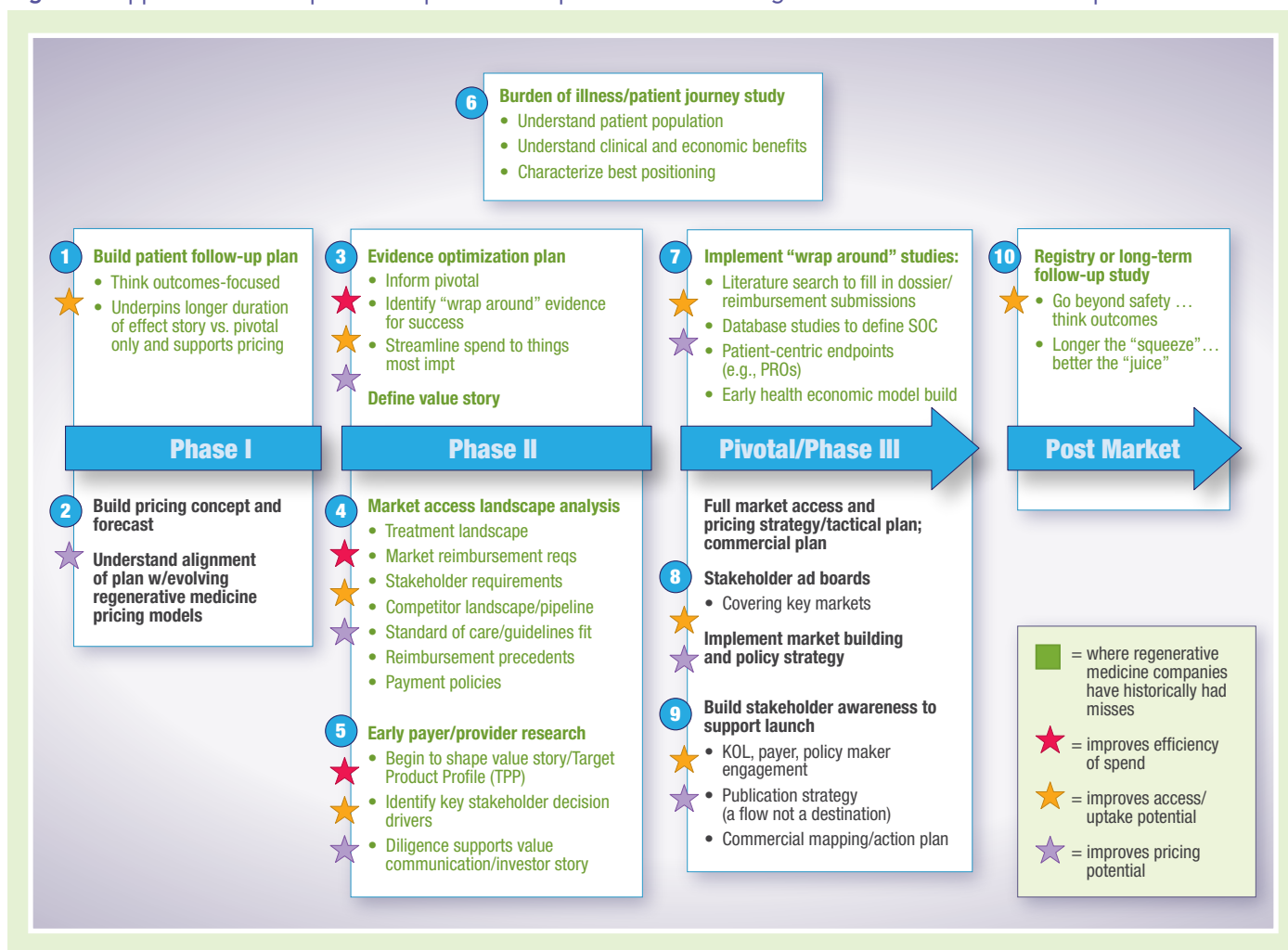
Abbreviations: ALL: acute lymphoblastic leukemia; BOI: Burden of Illness; SOC: Standard of Care; ADA-SCID: Adenosine Deaminase Severe Combined Immunodeficiency; OS: Overall Survival; CAR-T: chimeric antigen receptor T-cell; LPLD: lipoprotein lipase deficiency; PFS: Progression Free Survival

most important aspects (cited by 60-80% of respondents) of value demonstration in a recent payer survey lead by Faulkner and colleagues.²⁸ While simple in concept, the devil is in the details in terms of appropriately addressing these value dimensions in a manner that is aligned for the value challenges associated with novel regenerative and advanced therapies. Real-world evidence techniques have never been more important in painting a complete picture in this rapidly growing industry. Product developers that look beyond the potential for leveraging real-world evidence to support RMAT designation/fast tracking to

opportunities for building a value case acceptable to providers, hospital networks, health technology assessors, and payers will help ensure that their products are sufficiently differentiated to realize the promise that these transformative technologies have to offer the future of healthcare delivery. □

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Figure 7. Opportunities to Improve Acceptance and Uptake Potential of Regenerative and Advanced Therapies



Adapted from Faulkner E and Han D. Addressing Uncertainty in Regenerative Medicine Value Demonstration: What is Mission Critical vs. Mission Impossible? (Meeting on the Mesa, Alliance for Regenerative Medicine, La Jolla, CA, October 2016.); and, Faulkner E, Towse A, Husereau D, Carlson J. What Value Do We Place on a Cure? Value Demonstration Challenges Associated with Innovator and Regenerative Therapies in the EU, North America and Asia. (International Society for Pharmacoeconomics and Outcomes Research, 17th Annual European Congress, Amsterdam, Netherlands, November 2014).

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A Perspective on the 21ST Century Cures Act: Patient-Focused Drug Development

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Background

The 21ST Century Cures Act (Cures Act) includes several mandates designed to provide the U.S. Food and Drug Administration (FDA) the opportunity and resources to modernize their scientific and regulatory programs. The provisions address topics such as patient-focused drug development (PFDD); adaptive designs and statistical modeling in new drug applications; the use of real-world evidence to help support new indications for previously approved drugs and/or for post-approval study requirements; and, formalizing mechanisms for the Drug Development Tools Qualification program, among others. The Cures Act was signed into law December 13, 2016, and authorizes \$500 million in funding specifically for use by the FDA to carry out these and other provisions that fall within their purview.

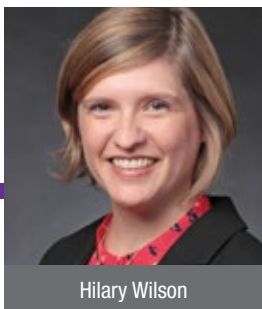
The “Patient-Focused Drug Development” section of the Cures Act (Title III, Subtitle A) emphasizes the need for patient engagement in drug development, and includes

provisions designed to define and standardize the use of patient experience data in regulatory programs.

Patient experience data is defined as “data collected by any person (including patients, family members, and caregivers of patients, patient advocacy organizations, disease research foundations, researchers, and drug manufacturers) that are intended to provide information about patients’ experiences with a disease or condition”.¹ The term specifically includes data regarding:

- a. The impact of the disease or condition, or a related therapy, on patients’ lives; and
- b. Patient preferences with respect to treatment of the disease or condition.”

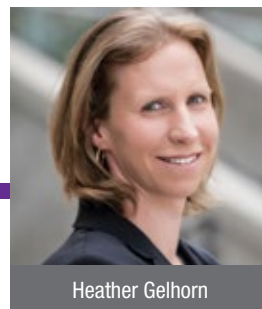
The legislation mandates that as of June 13, 2017, all new drug approvals include a brief statement summarizing any patient experience data that was submitted and reviewed as part of the application. The legislation does not specify the format or location in which the brief statement will be communicated to the public. The legislation does, however, require the FDA to release a series of new guidance documents that delineate methods, approaches, standards, and expectations for the use of patient experience data. It is reasonable to expect that the format and location of the brief statement for the patient experience summary may be defined in the guidance. In response to the mandate to develop the PFDD guidance, the FDA developed a plan for the issuance of seven new guidance documents related to the use of patient



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experience data over the next five years, and presented the plan to the FDA Science Board in May 2017.² With the approval of the Science Board, the FDA submitted their final plan for addressing the provisions of the Cures Act, including PFDD, to Congress in June 2017.³

Purpose

This paper is designed to provide an overview of the FDA's plan for issuance of the PFDD guidance² and discuss considerations for stakeholders related to the inclusion of patient experience data in drug development programs.

Model of Patient-Focused Drug Development

Patients who live with a disease are the ultimate stakeholder and are well-positioned to contribute to the comprehensive drug development process. The FDA's plan outlines a model for PFDD, which is designed to center the focus of drug development efforts on the patient (*Figure 1*). Patient perspectives should systematically be gathered to:

1. define the burden of disease, burden of treatment, and unmet needs,
2. identify the holistic set of impacts that are important to patients within a specific disease area,
3. identify and select meaningful clinical outcome assessments (COAs) based on the holistic set of patient-identified impacts,
4. define change in COAs that are meaningful to patients, and
5. characterize patient-acceptable benefit-risk ratios (*Figure 1*).

Historically, regulatory standards for patient experience data have centered on the use of patient-reported outcome (PRO) endpoint data in pivotal clinical trials. The content outlined in the FDA's plan for PFDD suggests that the new guidance will address alternate methods to gather patient experience data (e.g., patient stakeholder input, advisory boards, surveys, preference data) that may be used across the drug development cycle (i.e., pre-clinical through post-marketing).

The topics for the seven new PFDD guidances outlined in the FDA's plan describe patient experience data

as it relates to burden of illness, burden of treatment, impacts, meaningful clinical outcomes assessments, and patient-acceptable benefit-risk ratios. A description of each guidance document, as outlined by the FDA, is summarized below, followed by considerations for stakeholders.

Perspectives on the FDA's Plan for the Patient-Focused Drug Development Guidances

Guidance 1

Guidance 1 will be focused on methods and approaches to "collect meaningful patient input throughout the drug development process, and methodological considerations for data collection, reporting, management, and analysis."²

Considerations

As described in the FDA's plan, this first guidance is expected to highlight approaches to engaging with patients and collecting patient input throughout the entire drug development process. The proposed scope of this guidance highlights the importance of engaging with patients throughout a product life cycle through patient consultant services, surveys, advisory boards, interviews, and other research activities. This type of evidence may become acceptable information for regulatory submissions, so sponsors starting clinical programs need to consider engaging patients early and often.

Figure 1. Model for Patient-Focused Drug Development



In the absence of a guidance with defined acceptable approaches, sponsors need to focus on empirically-based methodology for collecting patient perspectives, and document any patient experience activities in a manner consistent with the rigor expected for regulatory submissions. Previous experience with the various types of FDA patient engagement work streams⁴ will likely inform the initial framework of this draft guidance. External stakeholders are encouraged to participate in discussions to help shape the guidelines. Feedback from stakeholders on methods used and associated challenges and successes can be communicated to the FDA during the public workshop and comment period. The first workshop to discuss the development of this guidance is December 18, 2017,⁵ and registration is currently open for in-person and web-based participation.

... the fact that a separate guidance will be released specifically to address methods and approaches for capturing the burden of disease and treatment suggests this may be an area of particular interest.

Guidance 2

Guidance 2 aims to delineate methodological approaches to “collecting comprehensive and representative patient and caregiver input on burden of disease and current therapy.”²

Considerations

Although there is some degree of conceptual overlap between this second guidance with the first, the fact that a separate guidance will be released specifically to address methods and approaches for capturing the burden of disease and treatment suggests this may be an area of particular interest. The FDA’s PFDD “Voice of the Patient” meetings⁶ are designed to systematically collect patient perspectives on the burden of illness, burden of treatment, and key impacts of disease. The initial framework for this guidance is likely to be influenced by the FDA’s experience with these Voice of the Patient meetings.

Sponsors are encouraged to refer to the publicly available Voice of the Patient meeting materials, which include audio files, transcripts, and reports, for disease areas in which these meetings have been conducted; leverage these materials when making decisions regarding medical product development programs; and, document these decisions. In disease areas where meetings have not been conducted, consider sponsoring an externally funded Voice of the Patient meeting⁷ to gather this information systematically in a manner that is consistent with the FDA’s methodology. Alternative approaches to consider collecting these perspectives include patient survey studies, burden of illness studies, patient journey maps, interviews, and focus groups.

Guidance 3

Guidance 3 will be focused on approaches to identifying a “holistic set of impacts that are important to patients” with a specific disease.²

Considerations

Again, there is some degree of overlap with this topic and the outline of the first guidance. The focus on “holistic” impacts suggest that the guidance may extend the range of outcomes and concepts considered in regulatory submissions beyond the traditional symptoms and physical impacts. The legislation requires the FDA to make a brief statement summarizing what, if any, patient experience data was submitted and reviewed as part of the application, but it is not clear where this information may appear. For example, will it appear in the product label? If not, what alternatives might be appropriate for communicating patient experience data?

The answer to these questions may not be addressed until the release of the guidance, but the FDA issued a draft Medical Product Communications guidance in January 2017⁸ that suggests PRO data may be used promotionally even when it is not in the product label, assuming it is for the approved/cleared indication in its approved/cleared patient population. This more flexible approach to the dissemination of PRO data is one indication that there may be a place for patient experience data in the era of PFDD that extends beyond the product label.

To capitalize on potential opportunities following the release of the guidance, sponsors should ensure that the impacts evaluated in medical product development programs are expanded to include critical targets of treatment as defined by patients. Sponsors should also leverage existing patient-defined core impact sets⁹ when available, and, when unavailable, consider partnering with other stakeholders to conduct patient workshops, surveys, Delphi panels, etc., to identify core impact sets that are important to patients.

Guidance 4

Guidance 4 is designed to define standards for the selection, design, and development of clinical outcome assessments and “will as appropriate, revise or supplement the 2009 Guidance to Industry on Patient-Reported Outcome Measures (2009).”²

Considerations

The plan for a new guidance on COAs that will be designed to either replace or supplement the existing PRO guidance¹⁰ may represent an expansion in regulatory thinking beyond the traditional PRO to broader patient-identified meaningful endpoints, which could be a performance-based measure, observational measure, PRO, or something else. The intent is to ensure that the COA is meaningful to patients.

The rigor of the evidence required to support a COA – the content validity, other validity, reliability, ability to detect change, and interpretation thresholds – is not likely to change. The FDA's outline for this guidance suggests rather an expansion to include other types of COAs, as well as specifications related to technologies that may be used for the collection, capture, storage, and analysis of electronic COA data. Sponsors with submissions including PRO endpoints may have the opportunity to negotiate certain aspects of their planned PRO strategy in the interim period.

Guidance 5

The fifth guidance aims to provide stakeholders with information required to “develop and submit proposed draft guidance relating to patient experience data for consideration by FDA” on patient experience related topics, for example “planning and conduct of clinical trials to be more patient focused, enhancing patients’ ability to enroll and continue to sustain participation in clinical studies, and the quality of their experiences as participants in such studies.”²

Considerations

The FDA has a recent history of working with disease foundations on disease-specific draft guidance documents and drug development tool qualifications.^{11,12} The new PFDD guidance is anticipated to leverage this experience and provide a formal guidance for stakeholders invested in defining best practices related to patient-centered drug development generally, as well as to those interested in undertaking efforts to develop and/or qualify endpoints in a precompetitive environment. This guideline seems to signal the FDA's readiness to continue to engage a broad range of stakeholders in the development of disease specific guidelines. In this context, collaborations of sponsors and stakeholders especially in the area of rare disease, may present new opportunities.

Guidance 6

Guidance 6 will outline how the FDA intends to respond to patient experience submissions, and timeframes for response to submissions made for the drug development qualification program for COAs and PROs.

Considerations

One challenge that stakeholders have encountered when engaging with the FDA outside the context of a drug development submission is the lack of a specified timeframe for response. The PFDD section of the Cures Act requires the FDA to issue guidance on how the Agency intends to respond to submissions related to patient experience data, including a timeframe for submissions that are not part of a regulatory application. Ideally, attaching specific timelines to precompetitive submissions will facilitate increased access to qualified measures for use in the drug development process.

Guidance 7

The final guidance is expected to define how the FDA intends to use “relevant patient experience data and related information, including with respect to the structured benefit-risk assessment framework” to “inform regulatory decision-making.”²

Considerations

This critical guidance is expected to define how the FDA will utilize the expanded patient experience data in the new PFDD regulatory framework. Although the specific requirements related to the use of patient experience data are currently unknown, the considerations outlined above provide a starting point for sponsors to consider as the guidance is developed.

This critical guidance is expected to define how the FDA will utilize the expanded patient experience data in the new PFDD regulatory framework.

The FDA's outline for this particular guidance highlights benefit-risk assessment framework. Although the methodologies acceptable by the FDA are not yet specified, it is reasonable to assume that developments in other areas of the FDA may be indicative of the potential direction of future initiatives. In the case of benefit-risk assessment, it is worth noting that the Center for Devices and Radiological Health (CDRH) recently released a guidance on the use and voluntary submission of patient preference information during the review process.¹³ This guidance was intended to acknowledge that patients and caregivers have their own perspectives and insights on diseases which may be important to consider from a regulatory perspective. The guidance also outlines preferred approaches and methodologies to gathering these types of data. It is conceivable that other FDA Centers such as the Center for Drug Evaluation Research (CDER) and Center for Biologics Evaluation and Research (CBER) may adopt, adapt, and/or expand this guidance to suit their needs, and that the current recommendations may be an excellent starting point for those wishing to capitalize on any potential opportunities early on.

The timeline for releasing the various PFDD guidance documents as outlined in the FDA's plan² is summarized in Table 1. The FDA will be holding several public workshops in advance of the release of draft guidance documents, and stakeholders are encouraged to actively engage in the process to help shape the PFDD regulatory guidance.

Conclusions

The issuance of this PFDD plan suggests that we have entered a new era of drug development where systematic inclusion of patients’ perspectives and experiences across the drug development cycle are an integral part of the

drug development and approval process. Going forward, methods and approaches for achieving PFDD are expected to be defined, and all new product approvals will be required to include a brief statement concerning what, if any, patient experience data were submitted and reviewed as part of an application. By leveraging empirically-based methods and approaches for capturing patient experience data, and by documenting the methods and approaches used, sponsors will be equipped to respond to and capitalize on the opportunities offered by the new PFDD guidance. Finally, by actively participating in the process planned by the FDA for the development of these guidance documents, all stakeholders can be satisfied that their perspective is considered in the development of these important documents. □

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Table 1. Timeline for Issuing the FDA's Patient-Focused Drug Development Guidance

Guidance	Workshop	Draft Guidance	Final Guidance
1	December 18, 2017	Q2 2018	Q1 2020
2	Q4 2018	Q2 2019	Q1 2021
3	Q4 2019	Q2 2020	Q4 2021
4	Q2 2019	Q2 2020	Q2 2021
5	N/A	Q1 2018	Q4 2019
6	N/A	Q4 2019	Q4 2020
7	Q2 2019	Q2 2020	Q4 2021

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U.S. Presidential Mandate on Value-Based Drug Pricing – Moonshot or Wormhole?

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What's old is new again, and value-based drug pricing is anticipated to be the cornerstone of a soon-to-be-released U.S. presidential executive order on drug pricing. Building on consultation with industry and government experts, the executive order is the policy follow-up to statements from President Trump's January 11TH press conference promising to "create new bidding procedures for the drug industry because they're getting away with murder" that will "save billions of dollars over a period of time." Simply by placing the terms value and pricing in proximity, the initiative generates hope that drugs will become a better value for patients and that recent examples of exploitive pricing (e.g., Daraprim, EpiPen) don't become a regular occurrence. But is value-based pricing really a prescription for large-scale savings?

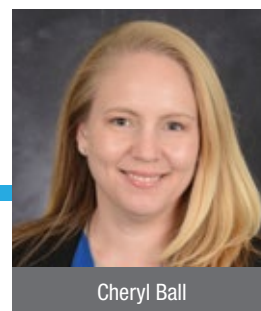
The concept of value-based pricing of pharmaceuticals is not a new one – it has appeared in many forms in different countries, including the U.K. and Italy, for more than a decade with many reported agreements in the U.S. over the last few years. Value-based pricing can also be referred to as outcomes-based pricing, performance-based risk sharing, or financial risk sharing. The approach is attractive for linking the price paid to achievement of specific outcomes or metrics, implying payment only for the value achieved or the risk avoided. It sounds empowering – a bit like the classic consumer money-back guarantee – but the reality is, of course, more complex. Imagine this model applied to the EpiPen. Would you be happy if Mylan, the maker of the EpiPen, simply paid you (or your heirs) and your health plan back for the cost of your EpiPen if the pen failed to work and you were rushed to the hospital? Would you be happy continuing to pay about \$600 for it every time your allergic reaction resolved as expected when it used to only cost \$100? Maybe not.

Value-based pricing models could allow payers to share the financial risk of a drug not working at all, not working as



well as planned, or not working well for every patient within their plan. Drug makers would pay a full or partial rebate of the list price of the drug based on the drug's real-world performance.

However, certain negotiating dynamics must prevail between payers and manufacturers to make value-based pricing agreements, well, valuable. Today, U.S. payers offering commercial and Medicare Part D plans generally negotiate rebate agreements, often volume-based, with drug manufacturers based on their internal Pharmacy and Therapeutics (P&T) Committee's assessment of a drug. These assessments are largely focused on evaluation of clinical trial data on efficacy and safety balanced against cost. The core of manufacturer-payer negotiation today focuses on balancing access restrictions against price concessions – essentially, what cost (in discounts or rebates) is the manufacturer willing to pay to make the therapy available to more patients, and how far is the payer willing, and able, to go to block patient access to the drug?



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For payers and manufacturers both to have interest in pursuing a more complex, value-based pricing arrangement rather than agreeing only on a simple discount or rebate for a specific drug, they must have both the means and the motivation to put an arrangement like this in place. That depends primarily on four factors, which are outlined below.

Since these conditions will differ across payers based on their experience, plan structures, and patient populations, as well as across manufacturers and individual drugs, a broad mandate on value-based pricing will be difficult to construct, and likely even more difficult to put into action.

To date, use of these agreements in the U.S. has not been widespread, although a recent growth in use suggests increasing interest and importance on all sides. Assessing the number and content of value-based pharmaceutical pricing arrangements in the U.S. is challenging – the specifics of the contracts are highly confidential and both parties must be in agreement to make the deals public. As of June 2016, the University of Washington’s Department of Pharmacy reported a cumulative 46 U.S. performance-based risk-sharing agreements were tracked in their database since 1997, but with no indication of the number of those agreements still active.¹ Harvard Pilgrim,^{2,3} Aetna,⁴ Cigna,^{4,5} Humana,⁶ Anthem⁷⁻⁹ and others have all

Uncertainty	<p>Clinical evidence presents uncertainty</p> <p>Clinical trials with single arms, surrogate endpoints with weak validation, or data confounding create greater uncertainty regarding the benefits of a novel drug. If the U.S. Food and Drug Administration (FDA) becomes less stringent on clinical trial design, as proposed by the current administration, frequency of uncertain outcomes may increase. Managing the uncertainty associated with a drug’s potential benefit is the most powerful argument for value-based agreements, as there are likely to be dichotomous views on the probability of benefit, with greater optimism on the part of manufacturers and greater skepticism from payers.</p>
Control	<p>Therapeutic alternatives available</p> <p>Payers have limited ability to restrict when there are few or no alternatives available, and manufacturers have limited motivation to offer price concessions when they are the only game in town.</p> <p>Lack of mandates and protections</p> <p>Part D plans are subject to Centers for Medicare and Medicaid Services (CMS) rules on protected classes of drugs, such as those for transplant rejection. The coverage mandate may limit negotiating power.</p>
Incentives	<p>Unsuccessful existing rebates</p> <p>Payers will not be motivated to replace existing and proven volume-based rebates with less-certain performance-based agreements.</p> <p>Potential benefit exceeds operational costs</p> <p>Tracking patient use and outcomes is inherently more time consuming and costly than tracking prescription volume, and assessing the potential value and performance of treatments to inform contract design requires time and significant actuarial skill. Payers will need to expect worse outcomes than the manufacturer expects in order for both parties to agree to terms they each find acceptable.</p>
Implementation	<p>Outcomes must be</p> <ul style="list-style-type: none"> • Meaningful: Both parties must agree on a measure of interest, relevant to the drug and patient population, and relevant to cost or quality measures that impact a payer. • Measurable: Measuring the outcome of interest must be feasible within the payer’s covered lives and within the process of patient care, without adding significantly to provider or patient cost or time. • Proximal: With member turnover frequency generally assumed at two years and contract duration often shorter, outcomes that take a long time to mature may generate limited interest. <p>Appropriate use is manageable</p> <p>Both payers and manufacturers may be concerned about ensuring appropriate use, or at least accounting for it in an agreement. Use of the drug in the “wrong” population or in an unexpected way (e.g., intermittent vs. continuous) can impact performance and therefore financial outcomes.</p>

... performance-based agreements are increasing in prominence and may become an increasingly important tool for bridging the value divide for manufacturers introducing highly innovative therapies with great clinical promise, but limited immediate proof.

publicly announced that they've made such agreements for products such as Entresto, Praluent, Repatha, Trulicity and others. The frequency of announcements of contracts certainly seems to be increasing, but the number and scope (number of patients affected), as well as the impact on price, are not transparent in public disclosures. Regardless, the frequency is likely to continue to increase if only because there is public relations value in announcing agreements – pharmaceutical manufacturers get credit for being flexible on pricing, and insurers get credit for being innovative and tough negotiators for their customers and members. The impact of a broad government mandate will be interesting to observe, given the diversity of private entities and public players, at the national and state level, involved.

Value-based pricing is potentially a valuable solution to the financial risk associated with the uncertainty of a drug's performance in the real world, or over the longer term.

But how do we ensure that the starting point for the risk sharing is meaningful? Going back to the EpiPen example, where do we start the value-based negotiation, \$600 or \$100? Clinical groups like the American Society of Clinical Oncology, non-profits like the Institute for Clinical and Economic Review, and numerous other stakeholders are generating public debate on how we assess baseline drug value, but an outcomes-based contract that uses current prices as its starting point is not likely to yield much in terms of savings.

Gaining experience with value-based contracts is likely to increase in importance for both manufacturers and payers. If guidelines for regulatory approval are relaxed and the overall level of uncertainty on value increases, developing value-based agreements may become a more critical tool to enable payers and manufacturers to mitigate against the financial risk associated with data uncertainty. However, it is likely to take a long, long time – if that point can ever be reached or measured – before a presidential mandate on value-based pricing yields dramatic savings for payers or patients. Nonetheless, performance-based agreements are increasing in prominence and may become an increasingly important tool for bridging the value divide for manufacturers introducing highly innovative therapies with great clinical promise, but limited immediate proof. □

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Value Frameworks: Will They Work in the U.S.? What are Stakeholders Saying?

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Despite lack of formal adoption of value frameworks by U.S. payers, there is widespread assumption/conclusion that these frameworks are influencing U.S. payer behavior and that their influence will grow over time. Examples include but are not limited to:

HEOR academics/consultants: "U.S. payer feedback indicates that ICER [Institute for Clinical and Economic Review] assessments are likely to have an important impact on formulary decision making processes in the United States," from *Value & Outcomes Spotlight*.¹

Industry trade publications: ICER "will help the VA's pharmacy benefits management services office use ICER drug price assessment reports to decide which drugs to cover and to dicker with drugmakers and wholesalers on price," from *FiercePharma.com*.²

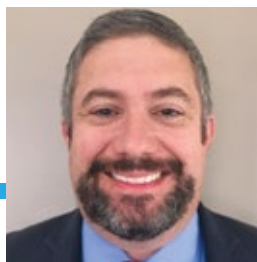
Advocacy organizations: There have also been claims that ICER helped block access to PCSK9s, e.g., "an obscure group called the Institute for Clinical and Economic Review, or ICER, is preventing and bogging down access to these types of medicines for patients in need," from a 2016 opinion piece by the head of the Hispanic Leadership Fund, *FoxNews.com*.³

Policy analysts: "According to longtime pharmaceuticals reporter Ed Silverman, 'ICER is becoming a de facto arbiter for the nation's medicine chest.' Take a closer look at ICER's *modus operandi*, and you'll see why this is a horrifying proposition. ICER, which holds itself out as a kind of *Consumer Reports* for drugs, is basically an industry-backed comparative effectiveness calculator. That ICER is [insurance] industry backed isn't the problem, it's that it uses comparative effectiveness to lend an air of legitimacy to the formulary shenanigans," from a 2016 column by Jeff Stier of the National Center for Public Policy Research, *USA Today*.⁴

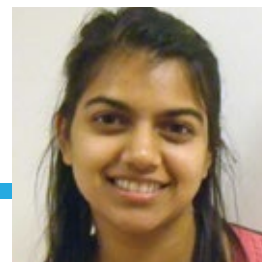
However, we are sceptical that value frameworks have been influential, or will be influential in the future.

For inline products, market forces are determinative. One payer told us, "we certainly won't move something around on formulary, and ICER hasn't affected and won't affect contract negotiations. Especially if one manufacturer has a ton of market power, they'd laugh if I told them to give a larger rebate based on an ICER report."

Even for pipeline products, payers see many obstacles to the value frameworks:



Mike Epstein



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"ICER is more of an ex-U.S. approach – P&T [pharmacy and therapeutics] doesn't talk about cost/QALY."

"The unfortunate reality is, a lot of big payers like PBMs [pharmacy benefit managers], they make a lot of their money on rebates. Does everyone have aligned incentives for low net cost and cost-effectiveness?"

"Where they will be potentially useful is if we can get more to the NICE example - you don't hit some threshold we can all agree on, you're not on formulary. But the U.S. is not a one-payer system, and the benchmark to ESI is different vs. United vs. my PBM. A fragmented system makes it more difficult to use these."

As a result, value frameworks have not had significant impact and are unlikely to do so in the future, as shown by a few representative U.S. payer comments.

"Usefulness of value frameworks has been modest at best."

"I've never gone after [manufacturers] with this. I've seen press releases and statements, but as formulary contract manager I can tell you I've had no specific conversations with any individual manufacturer if their drug isn't hitting a benchmark on an ICER report."

"On their value-based price benchmark, to be more applicable, instead of a QALY [Quality Adjusted Life Year] I want a WAC [Wholesale Acquisition Cost] or a net price per hard outcome achieved – something understood by P&T members."

The barriers to value frameworks in the U.S. fall into three categories.

Category 1: Structural/Systemic Barriers

Structural/Systemic Barrier 1:

Greater competition doesn't necessarily lead to higher value

First, competition with other insurers makes each insurer leery of being the first or only insurer to try to enforce the findings of value assessments – lest they lose business and fall prey to a public relations and stock price disaster.

"How would you like to be on the front page of a paper saying you're not paying for little Johnny's cancer therapy, and the boycotts, and the hits to your stock price? So you spend a few hundred thousand dollars on wasted effort to give false hope." – Medical director, top 10 national health plan

"The oncologist has to be the face of it. Memorial Sloan Kettering Cancer Center (MSKCC) said Zaltrap is not cost-effective, we're not going to pay for it, so the manufacturer renegotiated. If we did that, we'd be accused of being a death squad. Bad publicity. Bad PR could get the Department of Insurance looking at you, and bad articles, and you could get dropped by

oncology groups. Losing access to that network is a big deal because you don't have independent oncologists anymore." – Formulary and contracts manager, regional PBM

Second, competition doesn't necessarily mean lower prices as suggested by economic theory. In some cases, greater competition allows payers to play manufacturers against each other and extract price concessions (e.g., the Hepatitis C virus market). In other cases, each new product tends to set a new price benchmark which the next entrant takes as a new "floor" price. This is especially likely to happen where products are not seen as entirely interchangeable (e.g., categories like multiple sclerosis, in which payers value having multiple approaches available to prescribers and patients).

"The usual idea is more competition means lower prices, but in pharma whenever you get more competition, prices just go up anyways. Discussion is always like this: the prior product got x dollars so I want x + something. So more competitors means prices go up anyways." – Pharmacy director, regional affiliate of top 10 national health plan

Structural/Systemic Barrier 2:

Market dynamics may put payer in weak position

Political pressure, legal requirements, competition, any of a variety of forces at play in the U.S. market, may combine to put a manufacturer in a powerful bargaining position vis-à-vis a payer. This is especially the case if the manufacturer is "the only game in town" for a particular condition, usually an orphan condition.

"With some orphan drugs they just come and tell us how much it will cost, and that's that. Our PBM called an orphan drug-maker recently to discuss price and access, and they didn't even get their call returned." – Medical director, regional health plan

In other cases, the manufacturer wields tremendous power by virtue of utilization patterns.

"I could bring an ICER report to some manufacturer and tell them they need to charge me a value-based price, but if they have 50% market share, they won't give me the time of day." – Formulary and contracts manager, regional PBM

Thus, even if a value-based price and a manufacturer's bargaining position are at significant odds, there may be little a payer can do.

Structural/Systemic Barrier 3:

Perverse incentives are misaligned with "value"

Comparative clinical effectiveness may pale in comparison with the importance of price in payer decisions, even to the point of irrelevance in some highly saturated categories with many alternatives seen as interchangeable.

"Preferred drugs are preferred because the PBM gets more favorable pricing. It has NOTHING to do with anything clinical – at all." – Medical director, national plan (emphasis within quote is the payer's)

Even when it comes to price, the story is not simple. ICER has amended its method so that it uses an estimate of net price rather than list price – but even net price is not necessarily determinative of coverage/preference over clinically equal products, because the PBM incentive is to maximize its rebate revenue stream while keeping the price their health plan customers pay low. The PBM incentive is NOT to keep net cost low. This sometimes means preferring/protecting a product that has an interchangeable clinical profile with a much less costly alternative, but high share and impressive rebate revenue stream for the PBM.

"Incentives in our system aren't aligned for low net cost. Some PBM could prefer a product that's 2x dollars over a drug that's x dollars because the PBM gets a rebate that's twice as big with the more expensive drug."
– Pharmacy director, regional plan

Finally, co-pay cards interfere with value-based decision-making. Some plans refuse such cards because they interfere with the plan's efforts to share financial responsibility.

Structural/Systemic Barrier 4:

There are legal challenges to value-based decisions

Consider federal and state laws. Medicare protects access to all drugs in six classes (previously "all or substantially all" according to the 2003 Medicare Modernization Act [MMA], but the 2009 Affordable Care Act [ACA] changed to "all"): anti-convulsants, anti-depressants, anti-neoplastics, anti-psychotics, anti-retrovirals, immuno-suppressants. State Medicaid rules may guarantee access to low-value drugs as well; even technologies that fail to make the Preferred Drug List are obtainable through appeal.

"In Medicaid, normally state law requires that you cover all FDA-approved drugs. You can't not cover it, period. We've had plenty of examples [of drugs] with less evidence, things that are just bad for patients that we've had to cover – think about bone marrow transplant for breast cancer... Also, just because we don't put a drug on formulary, doesn't mean a person can't get it. They just have to go through more hoops."
– Medical director, regional health plan focused on Managed Medicaid

Category 2: Normative/Cultural Barriers

Normative/Cultural Barrier 1:

Frameworks and payers define value differently

There is no consensus among U.S. payers on the appropriateness of the cost/QALY metric, let alone on the widely cited \$50K/\$100K/\$150K per QALY thresholds.

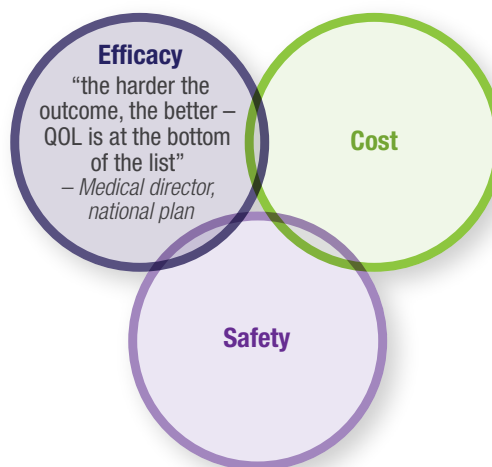
There is no consensus in the U.S. on the appropriateness of Bentham-style utility maximization; rather, there is a widespread consensus around the notion of 'no patient left behind,' like no child left behind in education. There is consensus among most U.S. payers that quality of life, a key part of the metric ICER hangs its hat on, is 'uninsurable' – employers, who sponsor the majority of insured in the U.S., do not assign high value to it in most categories.

"We don't value quality of life because the employers don't value it. Self-insured employers, if you say this might be better for your employees because they'll have better QOL on some metric, they look at you like you have three eyes. Only if it costs the same as another option, then they say okay. They're not interested in paying for it. In a 20-year span, behind closed doors I've never heard anyone say they would pay for better quality of life... How the employer defines value – the lowest cost they can get. Publicly they will define it differently, but privately, lowest cost." – Medical director, regional affiliate of a national plan

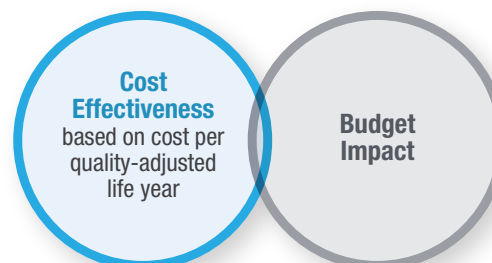
Another problem, a serious one for ICER, is that most providers do not accept the ICER metric as meaningful.

"The best way to get a physician to tune out is just talk about QALYs. Some don't know. None care. P&T doesn't care, either." – Pharmacy director, regional health plan

U.S. Payer Definition of Value



ICER Definition of Value



Normative/Cultural Barrier 2:

Frameworks compete with established approaches

Value frameworks didn't emerge into an environment with no history of consideration of value for money. To quantify value, some U.S. payers already calculate cost per outcome – the metric which is meaningful to them since it incorporates hard endpoint while excluding QOL.

"We divide into delta vs. placebo for each drug the net cost for some given time period on the key metric – HbA1c, ACR 50 or 70, ARR in MS, SVR in HCV – this is cost per outcome. That's what we care about so that's what we do in our P&T process." – Formulary and contracts manager, regional PBM

"Value? It's just efficacy divided by price. But it's hard to know what efficacy is in some areas. Pomalyst only had response rate, but no survival, for \$95-120K per year. The problem is, response doesn't mean you live longer." – Medical director, regional health plan

The new frameworks have to demonstrate they allow payers to achieve their goals (e.g., health plan: maximize profit) better than current approaches. Unless there is some structural change, frameworks also have to analyze the environment from the PBM perspective and show PBMs there is something in it for them.

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Normative/Cultural Barrier 3:

There are political challenges

Pressure from advocacy organizations and politicians can be more influential in payer decision-making than value defined by a value framework. Common examples payers offer are early cognitive behavioral intervention in autism, determining the minimum age for mammography, and Exondys-51 in Duchenne muscular dystrophy (DMD).

"The autism lobby has made rounds of state legislatures and been very successful in getting things covered for autism, like for early cognitive behavioral intervention that's never brought solid evidence it works. They can bypass that by going to the politician and saying it works, and it becomes more political than anything else, not value-based." – Pharmacy director, regional affiliate of top 10 national plan

"We're not using cost in our decisions; if we did, we wouldn't cover lots that we do, e.g., mammography – not politically correct, and the U.S. Preventive Services Task Force got shot down when they tried to raise the age limit." – Medical director, regional affiliate of top 10 national plan

"Exondys 51, the first drug for DMD, was approved and accelerated based on raising muscle dystrophin levels by 2% with no outcomes. Anthem said we won't cover, that hit the press, and now Anthem is back-pedaling. So when we try to bring value in, we get a lot of dirt on our faces." – Pharmacy director, regional health plan

"We also have to deal with people calling their U.S. senator and saying my son can't get the new drug for DMD, newspaper coverage, etc." – Medical director, regional health plan focused on Managed Medicaid

Category 3: Barriers Specific to Today's Frameworks

Framework-specific Barrier 1:

Frameworks have to influence prescribers too

Payers alone do not determine outcomes in U.S. healthcare. Payers consult heavily with key opinion leaders (KOLs) in most conditions. If KOLs disagree with the framework developer's approach and/or conclusions, or simply question credibility, frameworks will have difficulty affecting payer behavior. Payers also factor in the likely reaction to their policies by general prescribers. Payers report low awareness of ICER among rank-and-file prescribers; among those aware of ICER, payers perceive that prescribers question how ICER is qualified to guide medical decisions.

"ICER needs to do a better job on publicity and promotion and building connections to the clinical community. It's partly an awareness problem that people haven't heard of it on the clinical side. They also need to include clinical perspectives in their work as I have read assessments saying they're too actuarial and not clinical enough." – Medical director, regional affiliate of top 10 national plan

Today's frameworks credible to prescribers don't discriminate among drugs very well, while frameworks credible to payers discriminate but aren't credible to prescribers. Payers say that for a value framework to have impact, it must have a sufficiently strong reputation among all important stakeholders, including clinicians, and discriminate among therapies, selecting some as high-value and some as low-value, laying groundwork for covering some but not others, providing preferential coverage of some over others, etc. But there is a catch-22 – medical society frameworks have a good reputation with prescribers but don't distinguish. Frameworks developed by medical societies are viewed as slanted and non-discriminatory (e.g., the National Comprehensive Cancer Network [NCCN] gives almost everything they approve a 2A or better; see Table 1), although they are credible to prescribers and useful to payers as a foundation for rejecting drugs rated as poor by the framework. On the other hand, third-party frameworks (i.e., ICER) discriminate but are not credible to prescribers. ICER is seen as more objective by payers, but to date has little, if any, credibility

in the eyes of prescribers who are aware of it. ICER is seen as too actuarial and not clinical enough in terms of who developed it and the analyses themselves.

"Usually we don't look at the value frameworks because they almost seem to be self-serving. ICER is probably more neutral. The ones that are provider-based, it's difficult to accept they're all being altruistic and are trying to be in the best interest all around." – Medical director, regional health plan

"A majority of the clinical community would look on ICER as a non-clinical, insurance industry-based entity that doesn't have clinical credibility." – Medical director, regional affiliate of top 10 national plan

"Manufacturers spend a ton of money with ASCO. That makes it susceptible to a certain level of influence." – Medical director, regional affiliate of top 10 national plan

Table 1.
NCCN Categories of Evidence and Consensus⁵

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

Framework-specific Barrier 2:
ICER reports have come too late to effect change

To date, ICER's reports come too late to affect initial formulary placement. By the time initial formulary placement is set, market dynamics take hold and position is difficult to change later simply due to a value framework report. Timing issues – and the extent to which they are addressable – differ by the subject of the framework report. For pipeline products, payers typically make coverage/management decisions for high-profile products before FDA approval; they need to be ready when prescriptions come in, as an individualized process has unbearable transaction costs. ICER reports on pipeline products have come out too late to inform these decisions. ICER is

reportedly going to begin issuing pipeline product reports earlier, i.e., two months before the Prescription Drug User Fee Act (PDUFA) date. While issuing the reports earlier will help with the timing barrier, it will not help with the other barriers noted. For inline products, payers foresee little to no impact of reports on established categories. By the time the reports come out, member and provider utilization patterns and preferences are set, as are contracts and rebate revenue streams, guidelines, etc. Little impact is expected beyond marginal price concessions for products whose manufacturers have little leverage.

Framework-specific Barrier 3:
Framework organizations are not injecting new data into the mix

The data used by value frameworks organizations like ICER are the same data available to any other third-party evaluation organization (e.g., the Agency for Healthcare Research & Quality [AHRQ], ECRI, Hayes, Blue Cross and Blue Shield Associations' Technology Evaluation Center [BCBS] Tec) and any payer, making framework developers' comparative effectiveness research (CER) redundant to work done for P&T. So, the comparative effectiveness research done by a value framework organization should arrive at the same general conclusions as those produced by any other entity – and that is exactly what we have seen.

"They're not doing new research. Also, for lots of products we don't have head-to-head, so they're doing meta-analysis. I like what they're trying to do, but we do meta-analysis, too, as do other third-party organizations, and all they're doing with their clinical comparisons is using what's public. So I don't expect any new discoveries." – Medical director, regional health plan

Also, among the small minority of plans that calculate/use cost per QALY, ICER cost-effectiveness analysis (CEA) is redundant to internal analysis.

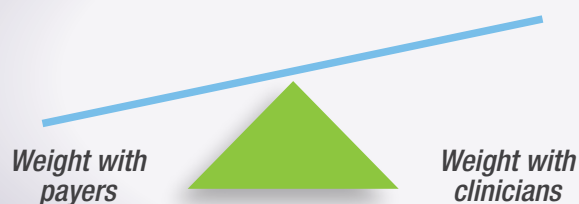
"With the PCSK9s, all the agencies like BCBS TEC, ICER, and the others did their analyses. My plan did its own cost-effectiveness analysis. Guess what? We all came to basically the same conclusion that plans which don't do CEA came to, which ICER also came to, which is that paying \$14K for these drugs doesn't make sense." – Pharmacy director, regional health plan

Framework-specific Barrier 4:
ICER's budget impact analysis: widely criticized by payers

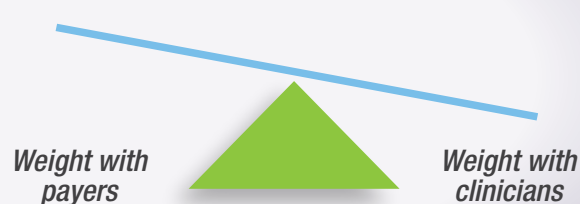
Payers neither devote nor want to devote a similar budget to each new drug, as profit maximization may dictate spending more on areas with large populations, greater disease burden, greater need, and/or higher drug quality/incremental benefit.

"With that budget impact analysis, ICER has the same \$900 million threshold for all drugs. But really, cancer should be different from diabetes." – Formulary and contracts manager, regional PBM

Payer-Focused Frameworks Like ICER



Medical Society Frameworks Like ASCO, NCCN



This criticism is related to U.S. payers' concerns about use of cost/QALY as a metric; a key underlying issue is that in the U.S. payers' view, one size does not fit all - not for budget impact and not for a value metric. U.S. payers consider each therapeutic category on its own merits, asking how a new product compares to standard of care in that condition – just as in Bismarckian systems in France and Germany. Payers also wonder how often the budget impact threshold is binding in ICER's analysis; most often, it seems to be the cost/QALY threshold that binds and "sets" the value-based pricing (VBP) benchmark.

Clinical Organization Frameworks

Although the ICER framework is viewed with scepticism by payers, clinicians, and other healthcare providers, there are other value frameworks which have been recently introduced. Prominent clinical organizations, such as NCCN – Evidence Block,⁶ American Society of Clinical Oncology (ASCO),^{7,8} European Society of Medical Oncology (ESMO) – Magnitude of Clinical Benefit Scale,⁹ and MSKCC – DrugAbacus,¹⁰ have introduced value assessment frameworks. The primary objective of these frameworks is to evaluate various oncology treatments, in terms of the health benefits offered and in some cases the cost of treatment.

The frameworks introduced by clinical organizations have not been formally adopted by payers; however, they are used for establishing treatment guidelines, guide shared decision making by clinicians and patients, influence policy decisions, and highlight disparity in the current drug price and economically justifiable price. Therefore, these assessments may influence, to some extent, treatment decisions by prescribers and patients. Furthermore, there are several studies in peer-reviewed journals reporting value assessments using one or multiple frameworks for competing treatment options.

Since each framework uses different criteria to assess the value of treatments, comparing results from the various frameworks is beneficial in quantifying the value of an oncology treatment which may be used alongside traditional cost-effectiveness analysis. For example,

Evidera has developed an oncology-focused tool to enable assessments of drugs using the frameworks developed by NCCN, ASCO, ESMO, and MSKCC. By assessing treatments using multiple perspectives, including payers, patients, and clinicians, an economically justifiable price can be estimated and a comparison against the spectrum of existing oncology treatments in the market can be provided. This helps with objection handling and communication of the treatment's value proposition to key stakeholders, such as clinicians, using standardized frameworks adopted by clinical organizations. Manufacturers may also conduct analysis across multiple indications and gauge the treatment's value proposition across their oncology portfolio.

Conclusions and Recommendations

For the vast majority of the U.S. payer market, our clients should watch for signs that barriers are falling. Regarding structural/systemic barriers, a key hypothetical event to watch for is whether the Centers for Medicare and Medicaid Services (CMS) gets involved and begins promoting ICER. Another sign would be loss of protection for the six protected classes, which seems unlikely given the political risk associated with displeasing elderly voters. In the normative/cultural barrier category, watch for ICER to reorient its analysis to use a value metric widely accepted by U.S. payers (e.g., cost per hospitalization avoided) rather than one crafted for a Beveridge-type single-payer system. This seems highly unlikely, given that ICER has recently reiterated its commitment to cost/QALY as the measure of cost-effectiveness due to widespread acceptance outside the U.S. Regarding barriers specific to today's frameworks, watch for ICER to gain in clinician awareness and credibility.

For the small number of plans that are reported to design formularies based on cost/QALY (e.g., Premera Blue Cross) and for provider entities bearing financial risk for drug spend (e.g., many Accountable Care Organizations [ACOs] in commercial, some in Medicare), manufacturers should critique ICER's approach, adapt CEA to the U.S., and argue for use of the adaptation over the ICER model. These tactics will also be helpful in managing the PR impact of organizations like ICER.

For ICER reports that concern an established product or class, deprioritize response. Health plans are highly unlikely to upset formulary status, contracts, rebate revenues, provider and member preferences, etc., simply due to an ICER report. For ICER reports on pipeline products, if they come out early enough to affect initial formulary placement, response should be a higher priority – but still with all the same caveats mentioned earlier.

Lastly, pay attention to other value frameworks being developed, such as those by clinical organizations. These

are currently focused primarily on oncology and are being used in treatment decisions and policy issues, however, they may eventually see adoption by payers and influence pricing and reimbursement decisions as well. In that case, value frameworks outside of ICER may be more impactful in the future. □

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Access Options for Investigational Products

Key Considerations

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Introduction

Patient access to an investigational product (IP) is available not only through the traditional means of clinical trials but also through various pre-approval access programs. These programs exist under a variety of names including extended access, open label extensions, compassionate use, special access, early access, expanded access, and named-patient programs.¹ Pre-approval access programs come in many forms and the regulations differ from country to country. These programs provide an important service in allowing select patient populations to receive an experimental drug which can thereby benefit both patients and innovators. Pre-approval access

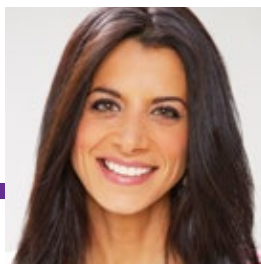
programs can be broadly separated into three categories: extended access (XAP), expanded access (EAP) and open label extensions (OLE).

Extended Access Programs (XAP)

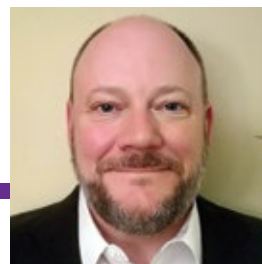
Extended access refers to the continued provision of an investigational product to clinical trial participants who were gaining benefit upon completion of the trial. Extended access programs, often referred to as compassionate use programs (CUP), provide a means to bridge the gap between the end of Phase II/III trial participation and country-level product approvals. Extended access programs are sought once a pivotal clinical trial has concluded, yet a large group of trial participants need to remain on the investigational product for therapeutic continuity. These programs also enable the ongoing collection of long-term safety data. The Declaration of Helsinki now recommends that post-trial provisions be made to provide access to participants who still need an intervention that is identified as beneficial during the trial.² Extended access programs can be submitted as an amendment to an existing investigational new drug (IND) application/approved protocol or as a separate IND/clinical trial application for this purpose.



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One method is to design a single, simple master study to allow access for all patients who are receiving benefit from the investigational product. Designing the extended access in this way is advantageous as it can allow the accommodation of patients from multiple parent studies to receive access under one protocol. The extended access program can have minimal data collection requirements, other than safety and the rationales for ending treatment, to ease the burden on trial participants. The new protocol can be implemented quickly by existing sites to coincide with patients completing the parent protocol to provide a seamless continuation of therapy. The programs often follow a more standard of care (SOC) approach to therapy compared with the more intense data collection required within the parent clinical trial(s).

For the innovators, extended access programs can offer an excellent opportunity to collect additional safety monitoring information as well as other targeted endpoints. Although little efficacy data is usually collected under extended access programs, for some rare diseases, these programs can significantly reinforce the efficacy and safety data collection. As with all clinical study programs, the risk of the study must be taken into consideration when designing the program. Concerns often exist around how the ongoing safety data will be managed and viewed by health authorities. This could complicate the evaluation of the safety profile by regulatory bodies during review of the marketing application. One method of addressing this concern is to plan for data analysis early and to ensure linkage of subjects to the parent protocol. Another potential concern for pharmaceutical companies is drug provision. The innovators often delay large scale production until later in the development process, therefore, supply of an investigational drug can potentially be limited. Diverting the supply to extended access programs might limit the availability for the other requisite trials.³ Other considerations for innovators include what type of reimbursement will be provided to study sites, if permitted per local regulations, and what is the exit strategy to conclude the program at market authorization. The innovators must ensure that clear strategies and plans are in place to address ongoing safety reporting and how analysis will be managed, drug distribution and provision, and an exit strategy from IP to commercial product.

Expanded Access Programs (EAP)

Expanded access programs refer to provision of an investigational product to broader patient populations who have exhausted other treatment options and potentially may gain benefit from the product following completion of standard clinical development, assuming the risk to benefit profiles are favorable. These patients are typically product naïve and did not participate in the clinical trial of the investigational product due to various reasons such as ineligibility, inaccessibility to trial locations, or closed enrollment of the trial. Expanded access programs are often referred to as “compassionate use programs” and

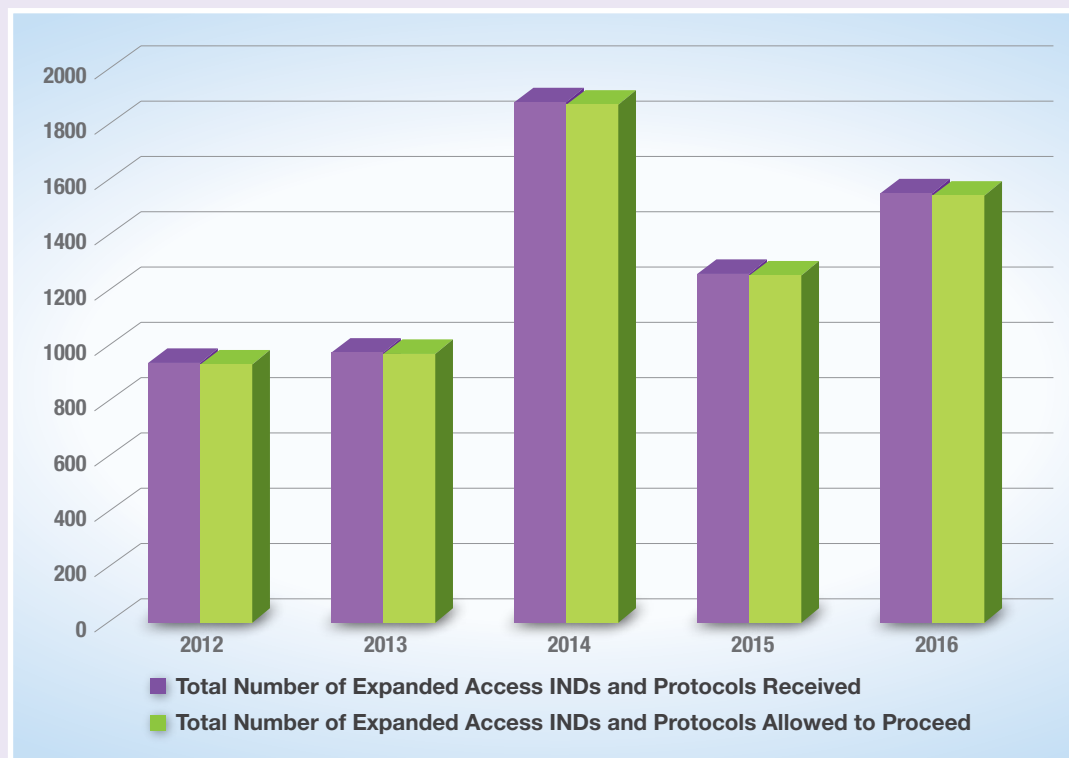
can be divided into two primary subtypes: named patient programs (NPPs) and treatment use protocols (cohort programs). NPPs exist under a variety of names in different countries but refer to programs that provide a single provision of an investigational product to an individual patient. Treatment use protocols involve providing a drug to a specified patient population.

Expanded access program requests have been increasing in recent years as demonstrated in Figure 1. Consequently, pharmaceutical companies are facing the need to establish new procedures to handle this increased demand. For example, in 2015 Janssen initiated a pilot program in partnership with the Division of Medical Ethics at NYU Langone Medical Center to develop a standardized review process for compassionate use requests with the goal of ensuring fairness, beneficence, and evidence-based decision-making. This partnership created the Compassionate Use Advisory Committee which consisted of an independent 10-person committee of physicians, bioethicists, and patient advocates to objectively advise on requests for daratumumab. From July to December 2015, Janssen received a total of 160 requests for pre-approval access. An initial screening by Janssen physicians determined that 76 of these requests were appropriate enough to send to the committee for evaluation, of which 62 submissions were selected for pre-approval access. This process enabled Janssen to provide an unbiased decision-making process to ensure the request was appropriate and in the patient’s best interest.⁴

Expanded access programs are intended to provide access to a patient population with a serious disease who have exhausted all commercial options and who meet the general eligibility of the clinical trial population but do not have access to a controlled clinical trial.

Expanded access programs are intended to provide access to a patient population with a serious disease who have exhausted all commercial options and who meet the general eligibility of the clinical trial population but do not have access to a controlled clinical trial. The design of expanded access or compassionate use programs should involve careful evaluation and planning, including the careful review of available data and a thorough assessment of the risk and benefit profile of the investigational product. Regulatory authorities such as the FDA and the European Medicines Agency (EMA) have specific definitions for these programs. For example, the FDA defines the program to be intended for treating a serious or life-threatening illness for which no other treatment is available, including randomized controlled clinical trials.⁵ The EMA provides a very similar definition, allowing EAPs for seriously ill patients who currently cannot be treated satisfactorily

Figure 1. Number of Expanded Access INDs and Protocols Received and Allowed to Proceed by the Center for Drug Evaluation and Research (CDER) of the U.S. Food and Drug Administration (FDA) (2012-2016)³



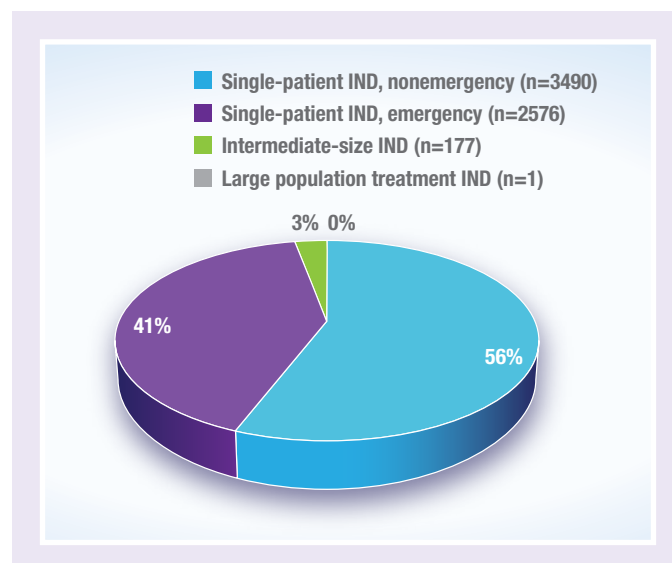
with authorized medicines or who have a disease for which no medicine has yet been authorized. However, in the European Union (EU), expanded access programs are coordinated by the member states which decide how and when the programs are implemented.⁶ Additionally, it is worth noting that EU regulation 536/2014, which is scheduled to go into effect in 2019, will change the approval structure of trials and will standardize processes between the member states.

It is also important to determine the type of program to be launched. In the U.S., there are three categories of expanded access programs in place: individual patient expanded access (named patient programs), intermediate-size patient population access, and expanded access for widespread use (treatment use programs). These programs are differentiated by the number of patients participating and the geographic distribution. Figure 2 demonstrates the relative breakdown of these different types of EAP approvals granted by the FDA from 2012-2016. NPPs accounted for the overwhelming majority of these approvals with more non-emergency use than emergency use. For each category, the FDA allows regulatory submission as either a new investigational new drug application (IND) or a protocol amendment to an existing IND.³

Additional considerations include global availability, the regulatory landscape, and requirements within the individual country. In the EU, compassionate use programs are coordinated by each member state and they are separate from named patient programs. The level of EMA

involvement is, therefore, different for each program.⁷ There is often a period of delay between when the sponsor receives the drug's first marketing authorization and the commercial launch of the product. How the expanded access program would be implemented should be factored into its development based on this timing. Other aspects to consider include the types of reimbursement provided (if any) to the site, the responsible party for managing drug shipment and supply, and how safety reporting will be managed. An analysis of 398 expanded access programs from ClinicalTrials.gov determined

Figure 2. Types of IND for Expanded Access Submitted to the CDER of the FDA (2012 - 2016)³



that 61% of these programs were industry funded. Most other funding sources came from university or academic sponsors.⁸ For investigational products in the late stage of the developmental cycles, having an exit plan in place could provide patients with safer and better transition from the program. This could include implementing a patient assistance program once the investigational product has been approved and commercialized. The timeline for provision of the drug until commercialization is also important to communicate in the guidance.

Open Label Extension (OLE)/Long-Term Extension (LTE)

Open Label Extensions (OLEs) are typically linked to a specific pivotal trial where there is a need to continue subjects on study drug and collect ongoing long-term data points at specific time points to meet health authority needs. The intention is to provide post-trial access for study subjects but with more monitoring rigor related to additional data collection. Figure 3 shows the frequency of published Open-Label Extension studies from 1996-2008.

An OLE is conducted to assess the long-term safety and tolerability of an Investigational New Drug but is also used for continued provision of unlicensed medicines after a randomized trial to patients with medical need of the investigational medicine.

Regulatory Background

From a regulatory perspective, extended access programs are still regarded as interventional trials. Full approval is required by regulatory authorities and ethics committees. The drug must be supplied by the sponsor with investigational product labeling compliant with local requirements (e.g., annex 13 of EU GMP guidelines). A full Clinical Study Report is required at the end of the trial. Promotion of the trial is permitted in accordance with

national regulations. Expanded access programs are a rather special case scenario from a regulatory perspective. Patient need must be clearly defined before access is granted. Most compassionate use programs in EU countries are initiated by the innovators; however, named patient programs are entirely initiated by physicians, who bear the liability. Physicians do not typically receive remuneration for their involvement in expanded access programs. Unlike XAPs, promotion of the availability of non-approved medications is not permitted for expanded access programs. Data collection requirements are also generally reduced for EAPs compared to XAPs.

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From a global perspective, the regulatory definitions and types of pre-approval access programs vary from country to country. Although the names often differ, these programs can generally be categorized under the three programs, as described above. For example, in Australia, the pre-approval access program is defined by regulatory bodies as the Special Access Scheme (SAS). The SAS program enables access to unapproved therapeutics for a single patient on a case-by-case basis.¹⁰ This corresponds to a named patient program under the definition of expanded access provided in this review. In the United Kingdom, there are two defined pre-approval access programs: Specials Scheme and Early Access to Medicines Scheme (EAMS). The Specials Scheme allows an individual patient to gain access to an investigational drug under the supervision of an authorized healthcare provider (i.e., name patient program [NPP]). The EAMS

Figure 3. Frequencies of Published Open-Label Extension Studies from 1996-2008

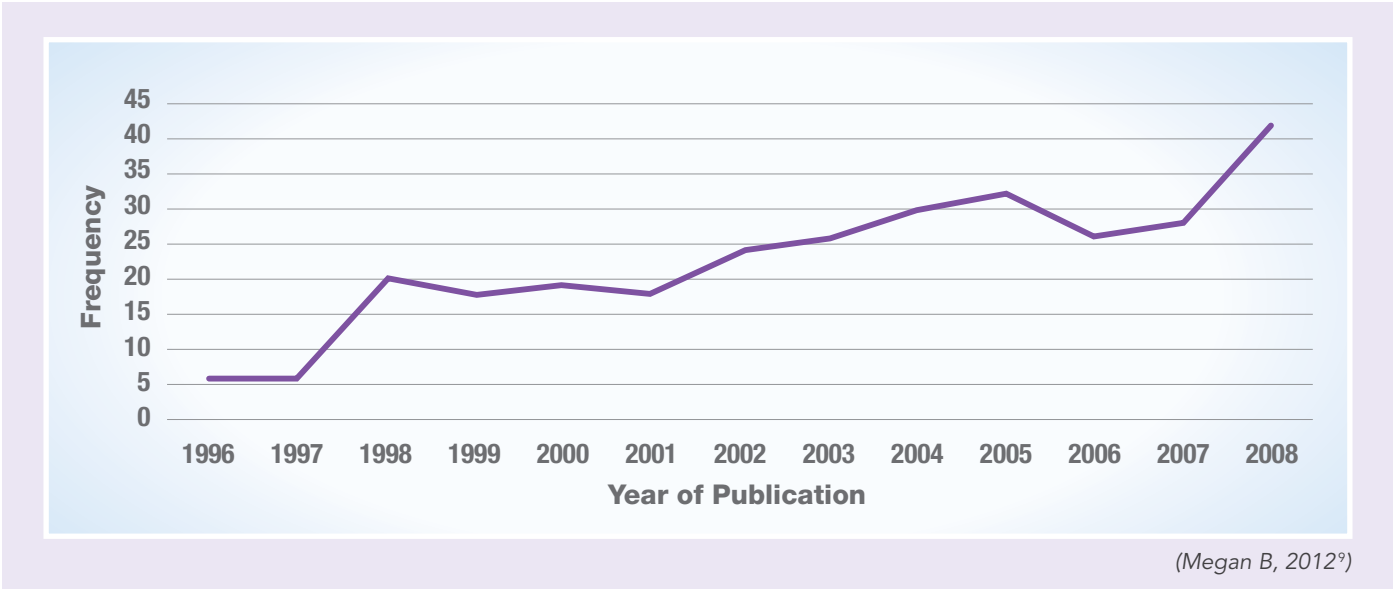


Table 1. Comparison Table of XAPs, EAPs, and OLE/LTE Programs

	XAP	EAP/CUP	OLE/LTE
Aim	<p>A single, simple study with these characteristics:</p> <ul style="list-style-type: none"> Manages the transfer of subjects from multiple controlled clinical trial programs into one “Platform/Master (XAP)” Designed to bridge the gap between the end of Phase III clinical trial participation and country level product approvals Allows continuity of therapeutic benefits 	<p>Initiated to provide access to patients with serious or life threatening diseases and meets these criteria:</p> <ul style="list-style-type: none"> Registration program has concluded There is clear evidence that the product will benefit a specific patient population Safety profile well described There is no other treatment option available, including controlled clinical trials 	<p>Typically linked to a specific pivotal trial and designed to:</p> <ul style="list-style-type: none"> Continue subjects on study drug when needed Collect ongoing long-term data points at specific time points, to meet health authority needs Provide a bridge of access for study subjects Provide more monitoring rigor related to additional data collection when required
Product-naïve patient	No	Yes	No
No other options	Potentially	Yes	No
Data collected	<ul style="list-style-type: none"> Safety (and minimal efficacy data) points Follows SOC while receiving IP 	<ul style="list-style-type: none"> Safety and Access 	<ul style="list-style-type: none"> Efficacy and Safety and Post-Trial Access Assessments and timing of assessments tend to follow Pivotal Program
Pros	<ul style="list-style-type: none"> Can close out ongoing clinical program sooner All patients move to one platform/master protocol and can be used for entire development program Typically moves subjects to SOC treatment Ability to collect limited data sets Sponsor can control the ongoing patient access more easily Follows normal regulatory process Multiple patient access Streamlined simple protocol Sites are normally reimbursed for the time spent managing the patient access – more site friendly 	<p>Treatment Use Protocol</p> <ul style="list-style-type: none"> Garner controlled safety data Multiple site participation Increases awareness of patient population and product <p>Named Patient Program</p> <ul style="list-style-type: none"> Less resources Can start quickly depending on the country Fits with a low number of requests No data collection 	<ul style="list-style-type: none"> Typically for Long-Term Data collection additional data Single extension per study
Cons	<ul style="list-style-type: none"> Follows normal regulatory process – can take longer to set up Access limited to subjects who participated in Controlled Clinical trial program 	<p>Treatment Use Protocol</p> <ul style="list-style-type: none"> Trial start times more closely mimic typical Phase II/ III trials Cost consideration versus demand <p>Named Patient Program</p> <ul style="list-style-type: none"> Does not allow all countries to have access in the same time Limited monitoring of safety Spontaneous requests are unpredictable Difficult to control access from a sponsor perspective Difficult to control numbers Physician holds regulatory responsibility and reporting often very time consuming and frustrating for them Regulatory process can differ for each country, no uniformity More work for the sites to set up the access Sites not usually paid – can get frustrated with work 	<ul style="list-style-type: none"> More data collection requires more rigor and resource to manage Costly programs Follows normal regulatory process – can take longer to set up Access limited to subjects who participated in Controlled Clinical trial program Single study per controlled clinical trial

enables a broader compassionate use program for patients with life threatening or seriously debilitating conditions.¹¹ In Japan, there are three programs for pre-approval access: Advanced Medical Care (AMC), Patient-Initiated Mixed-Care (PIMC), and Compassionate Use (CU).¹² These programs cover different patient populations under various circumstances but collectively provide for similar access to those previously described under EAPs and XAPs. Brazil also has multiple options to provide access to unapproved therapeutics. The Humanitarian Use Program allows patients to continue a therapy initiated in a local or foreign clinical trial after it has ended. The Expanded Access Program enables a cohort of patients to receive investigational drug products that are in Phase III trials in Brazil, or in a foreign country if that country has an established expanded access program. An NPP also exists for single patient use.¹³ These examples illustrate some of the differences that can occur between countries in their pre-approval access programs. Although the specifics and nomenclature often differ, many countries have similar pre-approval access programs to those defined by the FDA and EMA.

Ethical Considerations with Pre-approval Access

Although the FDA approves more than 99% of the applications submitted for expanded access, the regulatory process can be cumbersome and the pharmaceutical company employees, historically, are the ones providing the case evaluation and assessment.⁴ The concern for unknown adverse events and the desperation of running out of options create ethical challenges for the patient, treating physician, sponsor, and society as a whole. Though pre-approval access programs may have the intention of providing patients with increased options, patients may pursue these programs because they are desperate or have unrealistic expectations of the potential benefit. Manufacturers could also be hesitant to provide pre-approval access programs due to the program cost and potential liability for an otherwise promising drug. From a societal perspective, one of the major concerns of widespread pre-approval access is that it may reduce patient willingness to participate in clinical trials. This could compromise the integrity of the drug development goals of establishing safe and efficacious treatment options through evidence-based medicine.¹⁴ Another concern can be that pre-approval programs increase exposure to investigational products that may not ultimately be approved. A recent analysis indicated that 20% of investigational products with expanded-access INDs were approved within one year and only 33% were approved within five years after the initial submission.¹⁵ Although a variety of ethical concerns can arise from pre-approval access programs, they are becoming more common as patients have increasing access to information about potential interventions through the internet and social media. As the industry moves forward with more of these programs, these ethical concerns must be continuously evaluated and addressed. Successful examples have been demonstrated where

pre-approval access programs are established through an advisory committee, consisting of members from bioethics, patients, and advocacy groups to achieve a fair and unbiased program for evaluation of the requests.

Summary

Extended access, expanded access, and open label extension programs are important tools to provide different avenues for patients to receive investigational drugs. The need for these programs may increase as regulatory agencies and government bodies place greater emphasis on patient access as demonstrated by the wave of “Right to Try” legislation in the United States, including a bill passed unanimously by the U.S. Senate in 2017. The various pre-approval programs have different advantages and limitations as detailed in Table 1. Many parties are involved in these pre-approval access programs including patients, healthcare providers, pharmaceutical companies, institutional review boards, and regulatory authorities. Ethical and moral considerations from various perspectives compete at times, centering around the balance between patient autonomy and desire for access versus the societal consequences of providing unapproved investigational drugs. Successful real-world examples such as compassionate use or medical review committees have been established by pharmaceutical companies to address these concerns and will likely play an important role as these types of programs increase in public awareness. Real-world evidence can also provide a valuable tool by providing a basis to support use in disease states outside the approved indications. Electronic medical records and other “real-world” sources can help supplement existing clinical safety and efficacy data to provide a rationale for EAP approval. In countries where pharmaceutical companies can charge for EAPs, the price finalized during the EAP process can be used as a benchmark when the investigational product is approved and commercially launched. Moving forward, other considerations such as the influence of social media and internet medicine will also play larger roles in the implementation of these programs. □

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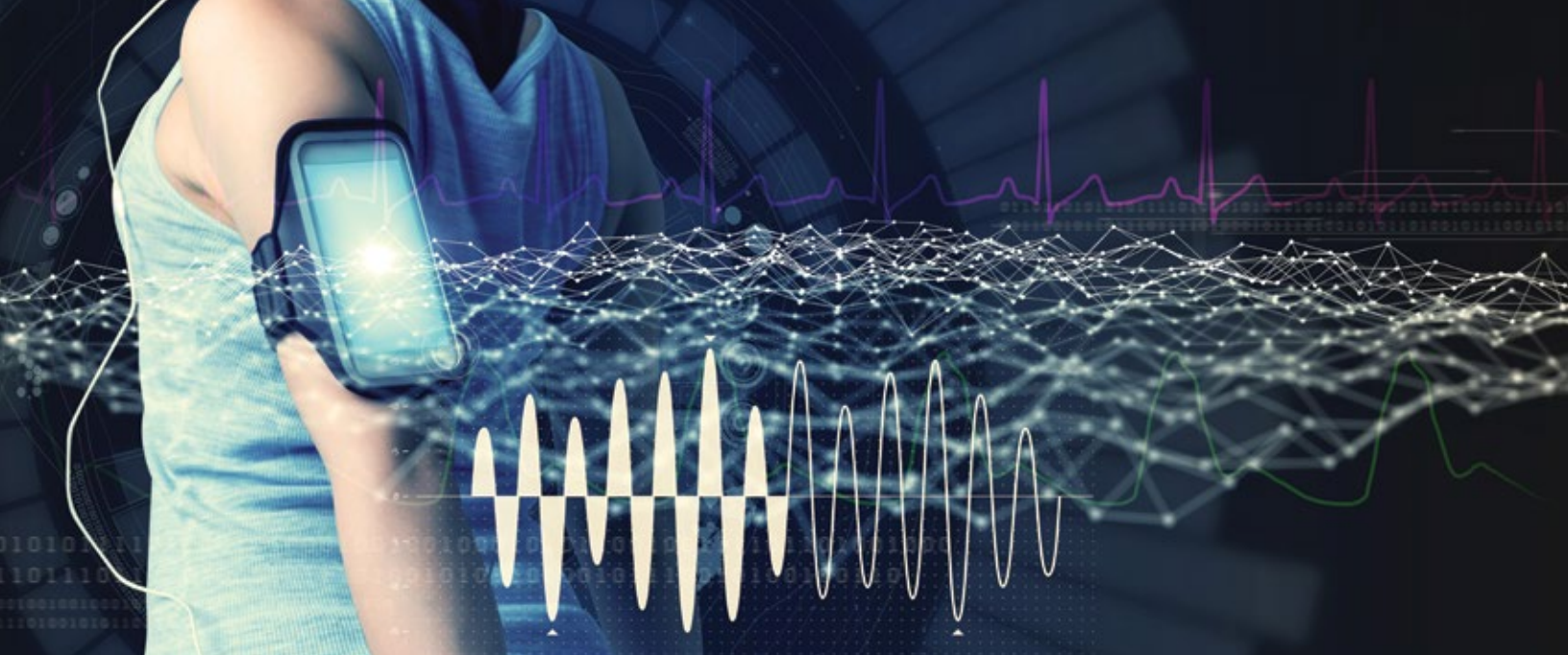
Special acknowledgment to the following people for their support in writing this article.

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Director Regulatory Affairs, Regulatory Affairs, PPD
Jodie Block, BSc
Director, Medical Affairs Research Operations, PPD
Robert Pope, PharmD
Fellow, Global Product Development, PPD
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Wearable Devices and Mobile Technology in Clinical Trials

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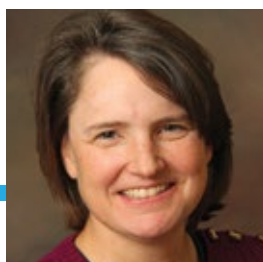
Wearable device technology has seen a rapid increase in market size over the last decade. The use of wearable device and mobile health (mHealth) technology in clinical trials has also increased considerably in recent years. The rapid evolution of this technology combined with patient-centric data generation provides cost-effective options for drug development. On the other hand, reliability and validation of devices and data, privacy concerns, and regulatory acceptance are slowing the integration of

these valuable tools as novel endpoints into clinical trials. Despite that, wearable devices and smart technology are transforming the drug development process.

Wearable Technology – Not a New Concept

Analysts at Gartner predict that 310.4 million wearable devices will be sold in 2017, an increase of 16.7% from units sold in 2016. \$9.3 billion of the \$30.5 billion revenue in the U.S. from wearable technology predicted for 2017 will be generated from smartwatches alone. By 2021, 504.65 million wearable devices are predicted to be sold.¹

This is not surprising since the fascination with and the history of wearable technology may reach back as far as the 17TH century when Cheng Dawei created the abacus ring. A small abacus was embedded into a silver ring and may have been used by traders.^{2,3} Although Leonardo da Vinci sketched a mechanical device that could be used to measure strides to aid road mapping, it was Abraham-Louis Perrelet in 1780 who invented the first pedometer to measure steps and distance walked. The pedometer was based on the automatic pocket watch mechanism that



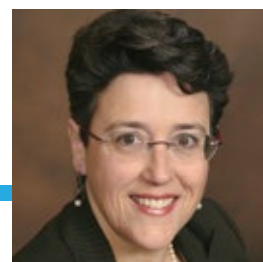
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winds itself up while the wearer is walking.⁴ Large-scale use of pedometers is credited to the Japanese walking clubs of the 1960s. At the time, a company produced the Manpo-kei – the 10,000 steps meter – laying the basis for the currently proposed health goal of 10,000 steps per day.⁵ The Fitbit, announced in 2008 and finally released in 2009,⁴ incorporated additional measurements such as heart rate, and estimates of calories burned and floors climbed. Wearables have evolved from the pedometer to a variety of devices such as watches, wristbands, chest bands, patches, headsets, and contact lenses that can measure a range of physiological parameters including steps taken, heart rate, electrocardiograms, glucose levels, and brainwaves, to name just a few.

The use of wearable devices in the clinic originated in the 1980s with the introduction of the Motionlogger®, a device the size and weight of a deck of cards strapped around the wrist to detect motion. These actigraphs were in regular use in clinical sleep research by the late 1990s.^{6,7} In August 2017, the National Institutes of Health clinical trials database returned over 170 results for the search term ‘fitbit’, over 300 for ‘wearable’ and over 440 studies for ‘mobile app.’ There is an exponential proliferation of collaborations between pharmaceutical companies and technology giants such as Apple, Google, and Microsoft, as well as start-ups, focused on the development of and applications for wearables and bio-sensing technology to support drug development in clinical trials and mHealth in general.

Today’s ‘wearables’ also called ‘wearable devices’ or ‘wearable technology’ encompass electronic technologies or computers integrated into clothing or accessories that can easily be worn. They generally combine sensors for biometrics and a communication capability that allows for data monitoring in real time and remote access to the data. mHealth or ‘mobile Health’ implements the use of mobile computing, monitoring devices, and communication technologies to monitor patient biometric parameters, as well as collect/maintain medical data and records by healthcare providers.⁸ Wearables and mHealth provide the advantage of direct ‘shareability’ of the data with relatives, friends, and, if the patient consents, the physician or healthcare provider. The data generated are specific to the patient and allow for personalized treatment decisions by a healthcare provider, or in some cases motivational support. The advantages for clinical drug development and healthcare in general are palpable. While this article looks at the advantages, uptake, and challenges for using wearables/mHealth in clinical trials, many of these apply seamlessly to the general healthcare of a patient particularly for chronic diseases.

Implementing wearable devices and mHealth into clinical drug development has many advantages, including reducing the burden on patients by decreasing or even eliminating follow-up visits to research centers, and allowing data collection over a wider window of time to

provide complete tracking of physiologic parameters, medication administration, and adherence to clinical study activities. The true benefit of wearable devices and the implementation of digital/mHealth lies in the advantages afforded to patients, investigators/trial sites, and sponsors.

What Does the Implementation of Wearables/ mHealth in Clinical Trials Offer?

Over the last few decades, access to quality medical care has improved and contributed to increased longevity. However, with longer lives, the incidence of chronic diseases increases, thereby further burdening healthcare professionals. Avenues to more efficiently manage patient care and data collection in clinical trials are required. The implementation of wearable devices and mHealth may alleviate some of the pressure on healthcare professionals by empowering patients to self-monitor, reducing the necessity for frequent visits to healthcare facilities and providing more data and behavioral insight for the drug development process.

Reducing the burden of healthcare-related tasks may be the largest benefit for patients. The broad familiarity of consumers with devices like the Fitbit, Jawbone, smartwatches, and smartphones facilitates the integration of similar devices specific for healthcare applications. The ability of a device to deliver prompts for various tasks, encourage medication dosing compliance, and to share physiologic data adds convenience to any treatment program.

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A PPD study employing two devices, a blood pressure cuff and an activity monitor connected to the patient’s smartphone, showed that patients were more comfortable using the consumer device that they are already familiar with rather than a device provided by a clinic or sponsor. Generally, patients are more comfortable using a device they already own versus using a study-specific device provided by the investigative team.⁹ Additionally, devices/apps that provide good documentation, quality of care options, and enhanced communication with a provider increased patient confidence and compliance with their treatment and care.¹⁰

Wearable devices continuously record the data in real-time and enable investigators and healthcare providers to track clinical trial participant status between site visits. Instead of using data gathered during a brief office visit

with various short tests such as a six-minute walk test for mobility, wearable devices allow for collection of movement data continuously over the entire observation period of the trial. This process contrasts significantly with the prior traditional method that required office visits for testing or the review of diary entries. Using wearable devices, available biometric and activity measures can be collected automatically, adding consistency and accuracy with time-marked data. Since most wearable devices are paired with a mobile app for data logging, care providers or investigators can remotely access the data collected by the device to efficiently reduce the number of office visits or even eliminate the need for office visits.

The use of wearable devices and access to the stored information allows healthcare providers and clinical researchers to gain additional insight into a disease process and participants' response to treatment.

The use of wearable devices and access to the stored information allows healthcare providers and clinical researchers to gain additional insight into a disease process and participants' response to treatment. Subjective participant data that might be influenced by a participants' status will be replaced with the objective data collected by the device. Real-time data access may aid signal detection and early detection of adverse events and facilitate decision making by a care provider or researcher on treatment adjustments based on the data collected.

Similarly, sponsors developing drugs also benefit from the implementation of wearables/mHealth into clinical trials by taking advantage of device capabilities to provide patient data that may be helpful in the development of new treatment options. Wearables today are more sophisticated and accurate, and measure a wider range of biometric and physiologic data, which can effectively characterize disease severity and progression.

Collected individualized data and the identification of population subsets responding more favorably to a medication (i.e., precision medicine) can contribute further to the understanding of the disease and targeted treatment development for the above or below average responders. Additional insight into various disorders may provide the opportunity to establish more sensitive measures of disease assessment through the better understanding of symptoms provided by the digital data.

Partnerships between the Pharmaceutical and Technology Industry

Companies outside the healthcare sector appreciate the utility of wearables and are increasingly getting involved

by providing tools to harness the possibilities wearables and mHealth provide for clinical trials. Apple developed ResearchKit, open-source software that allows researchers to create mobile apps supporting efficient data collection specialized to therapeutic area. CareKit, another open source framework provided by Apple, allows for the development of apps to assist patients to manage their own healthcare more efficiently.¹¹

Qualcomm, perhaps best known for the Qualcomm Snapdragon in smartphones, offers the medical grade, FDA quality 2net™ Connectivity Platform that enables healthcare connectivity and integration for hospitals, at home, and on-the-go care. Medical device data management is secure, rapid, and compliant to HIPAA privacy standards.¹²

Although the two technologies are very different, both play an important role in the overall wearable device integration into healthcare and clinical trials. Apple provides platforms for the development of customized apps for data collection and Qualcomm's 2net™ platform ensures secure storage, connectivity of devices, and accessibility to data.

Collaborations between pharmaceutical and technology companies have also sprung up recently. In 2016 Novartis teamed with Qualcomm to develop internet connectivity to deliver data directly to the cloud for its inhaler to monitor the use of the drug Onbrez® in patients who have COPD. A launch of the device is planned for 2019. In 2017, Novartis signed a deal with EU-based Propeller Health to use Propeller's digital platform with its inhaler.^{13,14}

Blood sugar level monitoring in insulin-dependent diabetes patients is another area where pharmaceutical and technology companies interface. A collaboration between Google and Novartis to develop smart contact lenses that can autofocus to correct vision issues and monitor blood glucose levels for diabetic patients was announced in 2014. It was initially expected to yield a commercial product as early as 2016. However, Novartis recently declared the project as high-risk and long-term.¹⁵

In 2016, Sanofi and Alphabet's (owner of Google) Verily Life Sciences company formed the joint venture Onduo to collect and analyze information from patients to improve diabetes care.¹⁶ Similarly, Abbott received European approval for its Freestyle Libre Pro™ continuous glucose monitoring system in 2015 and FDA approval in 2016. The sensor worn on the back of the upper arm eliminates the need for finger pricks and records data for up to 14 days.¹⁷

The opportunity for partnership is largest for chronic diseases that benefit from daily monitoring. Wearable devices are already available for monitoring patients with congestive heart failure, hypertension, sleep apnea, diabetes, and chronic obstructive pulmonary disease (COPD).¹⁸

Regulatory Oversight in the U.S. and Europe

In the U.S., the Federal Trade Commission (FTC) developed an interactive tool to guide sponsors developing mobile health apps to determine which federal laws may apply.¹⁹ Depending on the functionality, intended user, intended use, and risk, various laws overseen by the Office for Civil Rights (Health Insurance Portability and Accountability Act), Food and Drug Administration (Food, Drug and Cosmetics Act) and/or the FTC (Federal Trade Commission Act) may apply. For this article, we will only address the oversight provided by the FDA and the guidance issued.

In February 2015, the FDA issued an updated guidance for “Mobile Medical Applications” which supersedes guidance by the same name issued in 2013.²⁰ The guidance makes a distinction between mobile apps that will not fall under FDA oversight and FDA regulated mobile medical apps that meet the statutory definition of a medical device with the app intended to be used as a medical device or to “transform a mobile platform into a regulated medical device.” The FDA intends to exercise “enforcement discretion” for many of today’s wearable technology for health tracking by patients and/or healthcare providers. In July 2016, the FDA released guidance “General Wellness: Policy for Low Risk Devices” clarifying that the FDA does not intend to regulate ‘general wellness products’ defined as products that “are intended for only general wellness use” and present a low risk even if they meet the definition of medical device.²¹ However, wearable devices intended to diagnose or treat a medical condition would still fall under FDA regulation and would need to conform with HIPAA as a medical device. Even though a device may fall under the general wellness use and be outside of FDA’s regulation, if data from the device are used to inform clinical trial results, the data needs to be validated to ensure reliability and validity. The FDA is currently revising guidance to implement the clarification of the regulation of medical software provided by the 21ST Century Cures Act.²²

The FDA intends to exercise “enforcement discretion” for many of today’s wearable technology for health tracking by patients and/or healthcare providers.

Meanwhile, the European Medicines Agency (EMA) has not released any specific guidance addressing wearables or mHealth but has recognized the importance of their use for drug development. Opportunities for valuable data generation through wearable devices were discussed at a workshop to identify the opportunities of Big Data.²³ The new Medical Device Regulation clarifies that “software in its own right, when specifically intended by the manufacturer to be used for one or more of the medical purposes set out in the definition of a medical device, qualifies as a medical device, while software for general

purposes, even when used in a healthcare setting, or software intended for life-style and well-being purposes is not a medical device.”²⁴

The Clinical Trials Transformation Initiative (CTTI) released guidance on endpoint recommendations in June 2017. This public-private partnership of pharmaceutical companies, academics, and regulators such as the FDA are tasked with developing standards for the implementation of mobile technology in clinical trials. The CTTI established four project areas to identify challenges related to clinical trials using mHealth: legal and regulatory, stakeholder perceptions, mobile devices, and novel endpoints. The just released guideline advises that selection of novel endpoints should be guided by outcome measures that are meaningful to patients, the device should be selected based on the outcome measure determined, and endpoints should be selected using a systemic approach.²⁵

The above messaging regarding novel endpoints is key for wearable devices and mHealth. While the allure of the devices is certainly apparent, the matching of “fit for purpose” and endpoints that are clinically meaningful to patients is essential. As recommended by CTTI, select the endpoint first, then select a device. After selecting the device, additional validation work may be needed to demonstrate that the device indeed does measure the endpoint it was designed to measure in the target patient population. Such efforts are similar to the validation efforts of developing other clinical outcome assessments (e.g., FDA PRO guidance, 2009²⁶). Regulatory authorities are willing to consider wearable or mHealth novel endpoints, but will need to see the strength of evidence to support the endpoints.

In September 2017, the FDA announced the new Entrepreneur-in-Residence (EIR) program seeking entrepreneurs to work from the White Oak Campus at least three days a week to develop the Software Precertification Pilot. The Precertification Program, a mandatory part of the Digital Health Innovation Act,²⁷ will support the development of a tailored approach to software regulation. The software design and business metrics experts selected as EIR will analyze software business processes, model data collection, and determine regulatory requirements for the implementation of digital technology in clinical trials.²⁸

Challenges and Implementation

Reading the literature on wearable and mHealth implementation in general healthcare and its utility in clinical trials identified concerns on data standardization, analysis, and integration of data into existing information management systems; ownership and data privacy; and device-related technical limitations such as battery life, operational consistency, and accuracy. Additionally, there are also the human factors related to device usability such as consistency in wearing the device, following all prompts provided, and the general familiarity and uniform handling of the device and the included functions. However,

technology is evolving at an ever-faster pace and the challenges from yesterday are diminishing for today and tomorrow.

The implementation of wearable devices and mHealth could potentially bring economic advantages in the form of cost and time savings for patients as well as sponsors. Since potentially almost all monitoring and data collection can be done remotely through the connectivity of the device, the number of clinic visits can, at the least, be reduced significantly. In the best case, office visits could be eliminated completely. For the patient, this means less time to travel, less time spent at an office, and less time lost for daily activities. For the sponsor, it means less cost to cover physician time and travel cost reimbursement.

The sophistication and reliability of the devices has consistently and exponentially improved while the functionality with respect to the range of measurable parameters and the accuracy of the recorded data support the implementation of this technology in the clinical development process. The means for storing and analyzing the data are also being adapted to further support the implementation of this technology as a valuable research tool.

Conclusion

The use of wearable devices, smartphones, and mHealth provides an opportunity for real-time data generation and analysis to monitor a health-related condition, reduce the need for frequent physician office visits, and allow the collection of data required in the research and development of new medicinal products or medical devices. Although the integration of these applications is still challenged by regulatory uncertainty, data handling and analytic capabilities, as well as the complete integration into the research processes, these perceived hurdles are diminishing as the technology continues to improve. The full implementation of mobile trials soon will bring about the cost and time savings and return on investment sought by all stakeholders. □

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Real-World Studies Need Patients Too!

Unique Considerations for Patient Engagement and Retention

Krista A. Payne, MEd

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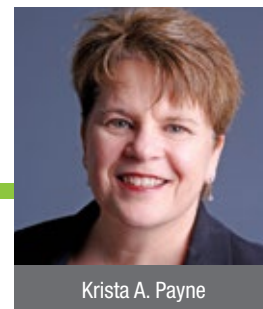
Patient-centric methods and approaches are integral to the design and execution of both interventional and non-interventional studies.^{1,2} From within the tightly controlled clinical trial environment to the real-world setting, data that provide patient insights on treatment outcomes and unmet clinical and humanistic need constitute critical evidence necessary for the successful market launch of novel and effective medicines.² However, without the successful engagement and retention of patients over the full duration of a study period, the quality and completeness of patient-generated insights and study data are at risk. Not surprising, the focus on “patients first” has become a critical component of early planning for study success.^{3,4}

If we define engagement as those design features or activities that elicit the patient’s interest in a study and that inspire their willingness to enroll and actively participate, then making the study relevant and meaningful to participants, including patients directly in the design process, and minimizing data collection burden, are study success factors of paramount importance. With respect to patient retention, once a patient chooses to participate, study processes and related activities must be patient-centric and serve to spark and sustain the patient’s interest and motivation to complete the study as required. Retention strategies are numerous and diverse and can include the development of patient communities or discussion forums, access to disease and health and

wellness resources, to fair market compensation for time spent attending study visits, and in the case of clinical trials, important access to novel treatments. Particularly in clinical trials, study visit reminders to reduce confusion and participation burden are also commonplace. The actual engagement and retention strategies and solutions employed will vary based on such factors as study type, design parameters such as duration and assessment schedule, as well as patient characteristics and disease manifestations.

For methodological reasons, patient-centric study engagement and retention solutions appropriate for clinical trials may not always be suitable for real-world studies.

In clinical trials, study protocols mandate study visits at fixed time points and pre-defined intervals to evaluate and compare drug efficacy across treatments. Frequently, a full suite of patient retention and support services spanning telephone or electronic visit reminders, to concierge-style transportation services and comfort kits that minimize burden and achieve complete data for all patients at all trial time points is employed. These approaches aim to ensure that a target sample size of patients attend all protocol-defined visits, and that all data are collected, to permit high quality and sufficiently powered analyses.



Krista A. Payne

Patient retention strategies and solutions in interventional studies do not impact the integrity of the trial design, nor the study results, as the trials are designed to achieve high *internal* validity under already artificial and highly controlled experimental conditions.

On the other hand, in real-world studies and registries, where drug *effectiveness* is the focus of investigation, it is paramount, methodologically, to avoid protocol-mandated study visits and patient retention strategies that could potentially alter real-world physician and patient behaviors. If, for example, the aim of the study is to better understand patterns of usual care and drug effectiveness and tolerability, then non-persistence to treatment, and missed medical appointments are, by nature, key outcomes of interest. In this scenario, the provision of multiple reminders and transportation to the study site to enhance patient engagement and data quality may actually result in improved treatment adherence – not as a function of the treatment itself, but rather as a result of aspects of the study protocol or related procedures. While minimizing patient burden is a hallmark of a patient-centric study, care must be taken in real-world studies to minimize the extent to which the engagement and retention of patients alters naturalistic behaviors and negatively impacts the external validity, or generalizability, of the results.

If solutions are NOT tailored to the observational study paradigm, then the integrity of the study data and results can be significantly compromised and applications for the use of these real-world data will be limited.

Differences between clinical trials and observational studies that have implications for the development and application of patient identification, retention, and engagement strategies are summarized in Table 1.

As a result of these fundamental methodological differences, non-interventional prospective studies and registries require engagement and retention solutions that can be markedly different than those applicable to interventional clinical trials. Key considerations for the development of real-world strategies and solutions are presented in Table 2.

Despite some inherent challenges, there are numerous important and effective over-arching strategies for engagement and retention of patients in real-world studies that can be implemented without necessarily impacting the integrity and external validity of the observational data collected.

- Consider the involvement of patients and/or caregivers in the study design process to better understand what may inspire patients to enroll, anticipate “pain points” for participants, and to inform the development or selection of study outcomes⁵
- Partner proactively with patient advocacy groups and other resources to
 - Inform study design and objectives
 - Align study with real-world, community-based resources that can provide information and support to patients and their families
- Establish study e-forums or on-line communities for study patients to connect with each other and share experiences
 - Consider employment of patient-centric on-line data entry platforms or “hubs” that integrate data collection with patient access to health and wellness links and other “connectivity” functions

Table 1. Summary of Key Differences Between Interventional and Non-Interventional Studies that have Implications for Patient Recruitment, Retention and Engagement Strategies and Solutions.

Parameter	Characteristics	
	Clinical Trials	Observational Studies
Robust Methods: Data Validity	Achieve high <i>internal</i> validity; selection criteria reduce variability in patient characteristics and treatment patterns to permit empirical evaluations of treatment efficacy	Achieve high <i>external</i> validity; focus on representativeness of uncontrolled usual care setting and generalizability of outcomes to broad real-world patient populations
Protocol	Moderate to high complexity; typically trial protocols are medical diagnostics and procedures heavy; schedule of assessments is fixed	Low complexity; diagnostics and procedures as per usual care; schedule of assessments is typically open
Treatment Patterns and Costs	Estimate costs associated with trial treatment arms to reflect cost differences in relation to mandated treatment protocols; treatment patterns are driven by clinical trial protocol	Evaluate naturalistic patterns and associated costs of care in the usual care setting; treatment patterns are driven by real-world physician and patient decisions not the study protocol
Treatment Adherence	Under <i>controlled</i> conditions, need to understand reasons for non-persistence (focus on drug characteristics: tolerability, lack of efficacy, etc.); data typically used to evaluate efficacy and to identify optimal dosing regimens	Under <i>uncontrolled</i> conditions, need to understand reasons for non-adherence and non-persistence (focus on drug characteristics and patient behavior); data used to evaluate effectiveness and to highlight unmet need in standard of care, including factors which may result in non-persistence, missed appointments, and treatment avoidance

- Minimize study participation burden for investigators and patients through simple and streamlined study protocols and related study procedures
- Develop case report forms that are restricted to “must-have” versus “nice-to-have” study variables
- Leverage technology to collect data directly from patients separate and apart from usual care visits with consideration given to “Bring-Your-Own-Device” (BYOD) approaches

In summary, a commitment to robust methods to achieve high quality and representative data does **not** mean that patient-centric study engagement and retention strategies cannot be employed for real-world studies. Careful consideration, however, of the trade-offs between the natural desire to control for complete study data at regular time intervals and adherence to core principles of real-world research that aim to avoid interference with usual care is clearly warranted. □

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Table 2. Key Considerations for Development of Patient Engagement and Retention Solutions

Focus	Key Considerations	
	Clinical Trials	Observational Studies
Investigator / Site Identification and Retention	Focus is on identification of high volume and research-savvy sites of care and clinical excellence; study budgets are substantial given need to manage investigational drug	Focus is on routine care sites in diverse settings; often research naïve; potentially harder to enroll; site contracts may take longer to execute; training materials may need to be more comprehensive but simpler in format; study budgets reflect fair market value for time and task spent on study activities
Patient Incentives to Enroll	Exposure to novel therapy (or hope of receiving if randomized to interventional arm) may drive enrollment; fair market value compensation for numerous clinical trial visits	Only fair market value compensation for usual care driven frequency of appointments permitted; patients must find meaning and relevance in the study
Patients	Track attendance for every scheduled clinical trial visit; missed assessments can be flagged and rescheduled	Track study visits as they occur; can't predict <i>a priori</i> at study launch when patients will attend or when they will miss visits as visit frequency is patient-specific and as per usual care
	Design and implementation of robust scheduled visit reminders; solutions and tools can be automated and technology driven	Cannot use additional reminders for usual care visits to study site as this will 1) prevent understanding of real-world patterns of care and patient and physician behaviors; 2) mask non-adherence and unmet need; and 3) impact patterns of care and inflate estimates of associated healthcare costs; reminders can be programmed for direct-to-patient questionnaires and diaries away from the study site
	Provide concierge-style transportation to study site to minimize study burden	Avoid use of aids to increase usual care visit attendance for same reasons as the need to avoid use of visit reminders
Technology	Use of patient attendance tracking tools and software to signal to the site when patient and/or physician outreach is necessary to resolve data gaps arising from missed visits	Tracking can be helpful to understand usual care visit metrics as study progresses but should refrain from using tool to alter pattern of usual care visits to study site

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SHORT COURSES

Sun., 5 Nov., 8:00 - 12:00

Using DICE Simulation for Health Economic Analyses

Instructors: Caro JJ, Moller J

Sun., 5 Nov., 13:00 - 17:00

Using Multi-Criteria Decision Analysis in Health Care Decision Making: Approaches and Applications

Instructors: IJzerman MJ, Marsh K, Devlin N

SYMPOSIUM SPEAKER

Tue., 7 Nov., 7:30 - 8:30

Changing the HTA Paradigm for Combination Therapies

Speakers: Ratcliffe M, Walker A, Jommi C, Edoo H, Caro JJ

WORKSHOPS

Mon., 6 Nov., 17:00 - 18:00

W8: Modeling Separate Lines of Treatment Versus Treatment Sequences in Cancer

Benedict A, Stevenson M, Sorensen S

Tue., 7 Nov., 8:45 - 9:45

W9: Patients' Preferences in the European Regulatory Environment: A Critical Review

Mühlbacher A, Marsh K, Van Til J

ISSUE PANELS

Tue., 7 Nov., 14:00 - 15:00

IP11: Determining Value in Health Technology Assessment Consistent with Societal Aims: Pursue New Options?

Caro, JJ, McGuire A, Litt M, Brazier J, Schlander M

Wed., 8 Nov., 13:45 - 14:45

IP24: Trusting the Results of Model-Based Economic Analyses: Is There a Pragmatic Validation Solution?

Caro JJ, Stevenson M, Moller J, Ghabri S

Wed., 8 Nov., 15:00 - 16:00

IP28: Patient Preferences in European Drug Regulation - Are We Ready?

Postmus D, Pignatti F, Demolis P, Tervonen T

FORUM

Tue., 7 Nov., 18:15 - 19:15

F2: Methods and Preliminary Results of the ISPOR Oncology Health Economic Modeling Special Interest Group

Muszbek N, Benedict A, Iannazzo S, Nabil Ashoush N, Qureshi H

PODIUM PRESENTATION

Mon., 6 Nov., 14:15 - 15:15

RM3: Methods for Extracting Treatment Patterns for Renal Cell Carcinoma (RCC) From Social Media (SM) Forums Using Natural Language Processing (NLP) and Machine Learning (ML)

Merinopoulou E, Ramagopalan S, Malcolm B, Cox A

POSTERS

SESSION I

PCN: CANCER

Mon., 6 Nov., 8:45 - 13:45

PCN46: A Systemic Literature Review of UK Epidemiology of BRCA1 and BRCA2-Mutated Locally Advanced or Metastatic Ovarian Cancer

Bedel D, Ricci V, Sarri G, Lavaud V

PCN59: Matching Adjusted Indirect Comparison of Sunitinib and Everolimus for the Treatment of Pancreatic Neuroendocrine Tumours (PNETS)

Ishak J, Rael M, Hicks M, Mittal S, Eatock M, Valle JW

PCN163: Cost-Effectiveness of Ibrutinib in Patients with Relapsed OR Refractory (RR) Chronic Lymphocytic Leukaemia (CLL) in England

Hassan F, Peng S, Dorman E, Sorensen S, Thompson G, Lee J

PCN165: Economic Evaluation of Nivolumab (NIVO) plus Ipilimumab (IPI) combination as First-line Treatment for Patients with Advanced Melanoma in Canada

Quon P, Xiao Y, Sorensen S, Schultz M, Tahami Monfared AA

PCN166: Modelling the Effectiveness of Ibrutinib Versus Physician's Choice (PC) in Relapsed OR Refractory (RR) Waldenström's Macroglobulinemia (WM) Within England

Guillermin A, Hassan F, Sydnor S, Peng S, Proskorovsky I, Sorensen S, Thompson G, Lee J

PCN200: Health State Utilities Associated with Treatment Options for Acute Myeloid Leukemia (AML)

Matza L, Deger K, Howell T, Hillgruber N, Yeager A, Hogge D, Fisher V, Louie A, Chung K

PCN221: Moving PRO Measures from the Promise to Impact in Oncology Clinical Practice: Results from a Systematic Literature Review

Anatchkova M, Skalicky AM, Whiteley J, Jagun D, McHorney C, Donelson SM

SESSION I
PDB: DIABETES/ENDOCRINE DISORDERS
Mon., 6 Nov., 8:45 - 13:45

PDB37: Cost-Effectiveness Analysis of Empagliflozin in the Treatment of T2D with Previous Cardiovascular Disease in Italy

Iannazzo S, Mannucci E, Reifsnider O, Maggioni AP

PDB56: Evaluating Patients' Preferences for Dulaglutide Versus Insulin Glargine Profiles in the United Kingdom: A Discrete Choice Experiment

Norrbacka K, Poon JL, Boye K, Thieu VT, Hassan SW, Gelhorn HL

SESSION I
PUK: URINARY/KIDNEY DISORDERS
Mon., 6 Nov., 8:45 - 13:45

PUK18: Sentiment Analysis of Social Media Posts from Renal Cell Carcinoma (RCC) Patients

Merinopoulou E, Ramagopalan S, Malcolm B, Lees M, Cox A

SESSION III
PCV: CARDIOVASCULAR DISORDERS
Tue., 7 Nov., 8:45 - 13:30

PCV115: The Effect of Changing Utility Elicitation Methods in Cardiovascular Disease: A Systematic Literature Review

Betts M, Rane P, Bergrath E, Chitnis M, Gulea C, Qian Y, Villa G

PCV166: Real-World Treatment Patterns Among Patients Initiating on Statins in England

Lambrelli D, Merinopoulou E, Donaldson R, Mardekian J, Hlavacek P, Tarasenko L, Masseria C, Hobbs FDR

SESSION III
PGI: GASTROINTESTINAL DISORDERS
Tue., 7 Nov., 8:45 - 13:30

PGI4: Incidence of Surgery for Inflammatory Bowel Disease Within 12 Months of Initiation of Vedolizumab or Infliximab

Patel H, Raluy-Callado M, Berger A, Carroll R, Khalid JM

SESSION III
PMD: MEDICAL DEVICES/DIAGNOSTICS
Tue., 7 Nov., 8:45 - 13:30

PMD105: Patient Preferences in Italy: Health State Utilities Associated with Attributes of Weekly Injection Devices for Treatment of Type 2 Diabetes

Matza L, Boye K, Jordan J, Norrbacka K, Gentilella R, Browne C, Federici M, Stewart K

SESSION IV
PHP: HEALTH CARE USE & POLICY STUDIES
Tue., 7 Nov., 15:30 - 19:15

PHP304: Challenges and Future Perspectives on the Reimbursement of Advanced Therapy Medicinal Products

Rothwell S, January D, Duda M, Gardner K, Michel S

SESSION IV
PND: NEUROLOGICAL DISORDERS
Tue., 7 Nov., 15:30 - 19:15

PND35: Cost-effectiveness Analysis of Peginterferon Beta-1a vs. First-line Injectable Disease-Modifying Therapies for the Treatment of Relapsing-Remitting Multiple Sclerosis in Spain

Ruiz L, Toro-Diaz H, Cele C, Hernandez L, Harrington A

PND36: Cost-Effectiveness Analysis of Daclizumab Beta Versus Fingolimod for the Treatment of Multiple Sclerosis from a Spanish Payer Perspective

Ruiz L, Marchado M, Toro-Diaz H, Xaplanteris L

PND39: Cost-Effectiveness Analysis of Dimethyl Fumarate Versus Teriflunomide for the Treatment of Multiple Sclerosis

Ruiz L, Marchada M, Toro-Diaz H, Cele C, Hernandez L, Harrington A

SESSION V
PIN: INFECTION
Wed., 8 Nov., 8:45 - 14:00

PIN22: Budget Impact of Introducing Ceftazidime-Avibactam for Complicated Intra-Abdominal Infection, Complicated Urinary Tract Infections, and Hospital Acquired Pneumonia Including Ventilator-Associated Pneumonia to a Hospital Formulary in Italy

Kongnakorn T, Tichy E, Merinopoulou E, Berto P, Di Virgilio R, Charbonneau C

SESSION V
PRM: RESEARCH ON METHODS
Wed., 8 Nov., 8:45 - 14:00

PRM13: Statistical Methods for Critical Care Outcomes

Exuzides A, Filonenko A, Kunz M, Gerlinger C, Chu BC, Bhurke S, Sites S

PRM62: Comparison of ICD-9 to ICD-10 Crosswalks Derived by Physician and Clinical Coder vs. Automated Methods

Simeone J, Bhagnani T, Rhodes T, Reynolds M

PRM103: Representing Uncertainty in Economic Evaluations: Getting More from PSA Results

Oguz M, Lanitis T

PRM127: Incorporating Dependence Between Model Parameters in Uncertainty Analyses

Oguz M, Roiz J

PRM133: Calibrating Model-Consistent Transition Probabilities for Fibrosis Stages in NASH

Gal P, Roiz J, Xiao Y

PRM207: Minimizing Bias in Parametric Survival Analyses of Published Kaplan-Meier Curves

Rael M, Ishak J

PRM217: An Accessible Comparison of Traditional Statistical and Machine Learning Approaches to Analysis of Real World Data: Which, When and Why

Merinopoulou E, Oguz M, Chu BC, McDonald L, Ulvestad M, Cox A, Ramagopalan S

PRM218: Minimizing Bias in Indirect Comparisons Utilizing Virtual Patient Level Data

Rael M, Isak J

PRM235: What's the Reality of Real-World Evidence in Health Technology Appraisal?

Sarri G, Lambrelli D, Gulea C, Gomez Espinosa E, Iheanacho I

PRM253: A Robust, Reproducible Method for Evaluating the Suitability of Disparate Observational Databases for Pooled Analysis, Using the OMOP Common Data Model

Reisinger S, McDonald L, Carroll R, O'Hara D, Anstatt D, Ramagopalan S

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Upcoming Presentations

Big Data in Precision Medicine

Oct. 31-Nov. 1, 2017; Washington, DC, USA

ISSUE PANEL

Real-World Data: A New Opportunity to Strengthen the Process

Flink B, Liu R, Luttringer O, **Spinner D**, Berliner E

SPEAKER

Evolving Real-World Evidence Approaches for Supporting Precision Medicine Access and Alternative Payment Models

Spinner D

jENS 2017

Oct. 31-Nov. 4, 2017; Venice, Italy

POSTER

Caregiver Burden Associated with Extremely Preterm Birth

Sarda S, **Lenderking W**, Pokrzywinski R, **Stringer S**, Mangili A

CTAD 2017

Nov. 1-4, 2017; Boston, MA, USA

POSTER

Validating Trial Power in Presence of Non-Random Dropouts Using Disease Simulation

Tafazzoli A, Quon PL, Stern S, Kansal A

5TH Annual European Advanced Therapies Investor Day

Nov. 9, 2017; London, UK

ISSUE PANEL

Health Technology Assessment and Access for ATMPs

Morgese P, **Faulkner E**, Kleinermans D, Pinilla-Dominguez P, Raffel H

IDF Congress 2017

Dec. 4-8, 2017; Abu Dhabi

POSTER

Evaluating Patients' Preferences for Dulaglutide versus Insulin Glargine Medication Profiles in Subgroups of People with Type 2 Diabetes

Thieu VT, **Poon JL**, **Gelhorn H**, Wasi-Hassan S, Norrbacka K, Boye KS

Recent Presentations

SMSNA 2017

Oct. 26-29, 2017; San Antonio, TX, USA

POSTERS

Patients' Perspective on the Impact of Moderate-to-Severe Genital Psoriasis

Clay Cather J, Potts Bleakman A, Naegeli A, **Poon JL**, Wallace A, Hollister K, Fretzin S

The Burden of Moderate-to-Severe Genital Psoriasis: Patients' Perspective on Symptoms

Ryan C, Meeuwis K, Potts Bleakman A, Naegeli A, **Poon JL**, Hollister K, Fretzin S

DIA Value, Access and Regulatory Strategy Workshop

Oct. 25-26, 2017; Basel, Switzerland

SESSION SPEAKER

How Can RWD Uncover Real Unmet Medical Needs in R&D Process?

Wasiak R

Benefit-Risk Assessment SIG

Oct. 24, 2017; ONLINE

<http://www.benefit-risk-assessment.com/marsh-webinar/>

WEBINAR

Do Patient Preference Have a Role in Health Technology Assessment? Current Practice and Future Potential

Marsh K

SMDM 39TH Annual Meeting

Oct. 22-25, 2017; Pittsburgh, PA, USA

SHORT COURSE

DICE Simulation for Health Care Decision-Analytic Modeling

Caro JJ, Moller J

ISOQOL 24TH Annual Conference

Oct. 18-21, 2017; Philadelphia, PA, USA

WORKSHOPS

An Introduction to Health-Related Quality of Life

Gelhorn H

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

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

POSTERS

Understanding Key Symptoms, Side Effects, and Impacts of HR+ and HER2-Advanced Breast Cancer: Qualitative Patient Interviews

Galipeau N, Klooster B, Krohe M, Tang D, Dillard S, Higgins S, Small T, **Revicki D**, Cella D

Translation and Linguistic Validation of the Psoriasis Symptom Scale (PSS) for Use with Plaque Psoriasis Patients

Parks-Vernizzi E, Arnold B, **Rentz A**, **Skalicky A**, Kaschinski D

ORAL PRESENTATION

Identification of COPD Severity Phenotypes and their Relationship to Symptom-defined Exacerbation Recovery: A Latent Class Analysis

Murray LT

2017 American Society of Human Genetics Meeting

Oct. 17-21, 2017; Orlando, FL, USA

POSTER

Acid Sphingomyelinase Deficiency (ASMD): Disease Impact on Families and Caregivers

Avetisyan R, **Hareendran A**, Sanson BJ, Tan S

World CDx Boston 2017

Oct. 17-19, 2017; Boston, MA, USA

ISSUE PANEL

Dx Strategy Considerations for Commercial Targeted Therapeutic Success

Sakul H, Emch J, Welcher R, **Faulkner E**, Wallar G

AMCP Nexus 2017

Oct. 16-19, 2017; Dallas, TX, USA

POSTERS

Budget Impact of Introducing Avelumab as a Second-Line (2L) Treatment for Locally Advanced or Metastatic Urothelial Cancer (mUC) in the United States (US)

Kongnakorn T, Benedict A, Barra M, Phatak H, Bharmal M, Kearney M, Galsky M

Budget Impact of Introducing Avelumab as a Second-Line (2L) Treatment for Locally Advanced or Metastatic Urothelial Cancer (mUC): a Medicare Perspective

Kongnakorn T, Benedict A, Barra M, Phatak H, Bharmal M, Kearney M, Galsky M

Treatment Patterns and Healthcare Resource Use in Migraine Patients Newly Initiating a Preventive Treatment: Interim Results from the Assessment of Tolerability and Effectiveness in Migraine Patients using Preventive Treatment (ATTAIN) Study

Kawata A, Shah N, Poon JL, Shaffer S, Sapra S, Wilcox T, Tepper SJ, Dodick DW, Lipton RB

North American Menopause Society Annual Meeting

Oct. 11-14, 2017; Philadelphia, PA, USA

POSTER

The Burden of Illness Associated with Symptomatic Vulvovaginal Atrophy (VVA): A Systematic Review

Kagan R, Martin A, Sarri G, Guo Y, Baradaran S, Harrington A

Risk Management Plan Summit

Oct. 11-12, 2017; London, UK

SESSION SPEAKER

Risk Minimization Measures: From Regulatory Framework to Practice

Rubino A

Evidence USA

Oct. 10-11, 2017; Philadelphia, PA, USA

PODIUM

Safer, Smaller, and More Cost-Efficient Clinical Trials: The Value of Biomarkers for Clinical Trial Enrichment

Simeone JC

MedAffairs Leaders Forum

Oct. 10-13, 2017; Berlin, Germany

SESSION SPEAKER

Data Strategy in the Ever Changing World of RWE and Medical Affairs

Wasiak R

Cell & Gene Meeting on the Mesa 2017

Oct. 4-6, 2017; La Jolla, CA, USA

ISSUE PANEL

Navigating Regenerative Medicine Technology Assessment and Reimbursement in North America and Europe: Charting a Path to Patient Access

Faulkner E, Cross J, Goldenring J, Powell R, Tolley K

IDWeek 2017

Oct. 4-8, 2017; San Diego, CA, USA

POSTERS

Associations Between Timeliness of Therapy and Clinical and Economic Outcomes Among Patients with Serious Infections Due to Gram-negative Bacteria (GNB): How Much Does Delayed Appropriate Therapy (DAT) Matter?

Bonine NG, Berger A, Altincatal A, Wang R, Bhagnani T, Gillard P, Lodise T

Evaluating Symptom Severity of Influenza Viral Infection Using the Influenza Patient-Reported Outcomes Instrument (FLU-PRO) in a Healthy Human Challenge Model

Han A, Poon JL, Powers JH, Yu R, Leidy NK, Memoli M

ORAL PRESENTATION

Carbapenem-resistant Enterobacteriaceae (CRE) or Delayed Appropriate Therapy (DAT)—Does One Affect Outcomes More Than the Other Among Patients with Serious Infections Due to Enterobacteriaceae?

Lodise T, Berger A, Altincatal A, Wang R, Bhagnani T, Gillard P, Bonine NG

Pharmacovigilance 2017

Sep. 27-28, 2017; Chicago, IL, USA

WORKSHOP

Does Real-World Evidence Have a Role in Pharmacovigilance?

Weiss S

Real-World Evidence

Sep. 27-28, 2017; Philadelphia, PA, USA

SESSION SPEAKER

The Promises and Pitfalls of RWE Data and Analysis Standardization

Reisinger S

Psych Congress 2017

Sep. 16-19, 2017; New Orleans, LA, USA

POSTER

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

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

ISPOR 6TH Latin America Conference

Sep. 15-17, 2017; Sao Paulo, Brazil

SHORT COURSE

Modelación Aplicada (Applied Modeling)

Caro JJ, Mejia A

ISSUE PANELS

Health Technology Assessments (HTA) and International Reference Pricing (IRP) - How's Pharma Preparing Themselves to Optimize Evidence and the Value of their Innovation?

de Bustamante MM, Caro JJ, Cristancho RA, Guarin DF

Multi-Criteria Decision Analysis (MCDA) in Latin America

Valentim J, Garau M, Caro JJ, Murta Amaral L

26TH EADV Congress 2017

Sep. 13-17, 2017; Geneva, Switzerland

ORAL PRESENTATION

Patient Perspectives on Symptoms of Genital vs. Non-Genital Psoriasis: A Qualitative Study

Meeuwis K, Ryan C, Bleakman AP, Naegeli A, Poon JL, Heredia EE, Jones CA, Cather JC

POSTER

Content Validity Assessment of the Psoriasis Symptom Scale for use in Patients with Moderate to Severe Psoriasis

Naegeli A, Poon JL, Anatchkova M, Heredia E, Burge R

ISSVD World Congress 2017

Sep. 13-15, 2017; Mendoza, Argentina

ORAL PRESENTATION

The Burden and Impact of Moderate-to-Severe Genital Psoriasis on Female Patients

Cather J, Potts Bleakman A, Ryan C, Poon JL, Malatestin B, Naegeli A, Fretzin S

ERS 2017

Sep. 9-13, 2017; Milan, Italy

POSTER

Danirixin Improves Respiratory Symptoms and Health Status in Mild to Moderate COPD - Results of a 1 Year First Time in Patient Study

Miller B, Lazaar A, Tabberer M, Yonchuk J, Leidy N, Ambery C, Bloomer J, Waltz H, Tal-Singer R

Recent Presentations - CONTINUED

IHC 2017

Sep. 7-10, 2017; Vancouver, Canada

POSTERS

Characteristics of Patients Newly Initiating a Preventive Treatment for Migraine: Baseline Data from the Assessment of Tolerability and Effectiveness in Migraine Using Preventive Treatment (ATTAIN) Study

Kawata AK, Shah N, Poon JL, Shaffer S, Sapra S, Mutebi A, Wilcox TK, Tepper SJ, Dodick DW, Lipton RB

Evaluating Clinically Meaningful Within-Subject Change in Functioning Associated with Migraine Prevention Using the Migraine Physical Function Impact Diary (MPFID)

Kawata AK, Hareendran A, Poon JL, Thach AV, Desai P, Kubo Y, Mikol DD, Dodick DW, Lipton RB, Tepper SJ

Reducing Impaired Days: Results from the STRIVE Trial, A Phase 3, Randomized, Double-Blind Study of Erenumab for Episodic Migraine

Hareendran A, Buse DC, Lipton RB, Bayliss MS, Mikol DD, Revicki DA, Zhang F, Desai P, Picard H, Kawata AK

Reducing the Impact of Migraine on Functioning: Results from the STRIVE Trial: A Phase 3, Randomized, Double-Blind Study of Erenumab in Subjects with Episodic Migraine

Buse DC, Lipton RB, Mikol DD, Thach AV, Desai P, Picard H, Kubo Y, Hareendran A, Kawata AK

2017 Duke Industry Statistics Symposium

Sep. 6-8, 2017; Durham, NC, USA

WORKSHOP

Data Missing Not at Random: Challenges in the Use of Real-World Data for Clinical Outcomes Research

Ishak J, Exuzides A, Blanchette C

ICPE 2017

Aug. 26-30, 2017; Montreal, Canada

WORKSHOP

Beyond Retrospective Studies, Using Electronic Health Records for Prospective Research

Koro CE, Weiss S, Curtis L, Hernandez-Diaz S, Davis KJ, Raine J

SHORT COURSE

Using Pharmacoepidemiology Database Resources to Address Drug Safety Research (DATA)

Hall G, Reynolds MW, Haynes K, Lanes S, Raman S

POSTERS

Incidence and Prevalence of Diabetes Mellitus among Children Aged 10-18 Years in the United States

Teltsch DY, Farsani SF, Huse S, Sicignano N, Brodovicz KG, Cristaldi C, Nordstrom BL

Natural History of Non-Alcoholic Fatty Liver Disease and Non-Alcoholic Steatohepatitis: A Longitudinal Assessment of Severity, Progression, and Risk Factors

Nordstrom BL, Simeone JC, Hoogwerf BJ, Li Q, Haupt A, Ali AK, Boardman MK, Bae J

Post-Authorisation Safety Study of Pioglitazone Use in Denmark Post Label Change

Cid Ruzafa J, Ulrichsen SP, Bennett D, Ehrenstein V

REMS Survey Response Rate by Stakeholder Type, Mode of Invitation Delivery, and Method of Completion

Veley K, Covington D, Sites S, Kinard R

Survey of Physician-Mothers' Facebook Group to Inform Pregnancy Registry Recruitment

Covington D, Veley K, Sites S, McKain L

Zika Virus: Implications for Pregnancy Exposure Registries

Covington D, Buus R

ORAL PRESENTATION

Study of Mirabegron and Cardiovascular Outcomes using the Publicly Available Mini-Sentinel Protocol

Simeone JC, Nordstrom BL, Appenteng K, Huse S, D'Silva M

77TH Scientific Sessions of the American Diabetes Association

Jun. 9-13, 2017; San Diego, CA, USA

POSTERS

Glycaemic Control in 14,005 Patients with Type 2 Diabetes Initiating Second-Line Therapy in 36 Countries: The DISCOVER Study

Khunti K, Arya N, Cid J, Fenici P, Gomes MB, Hammar N, Ji L, Kosiboro M, Pocock S, Shestakova MV, Shimomura I, Tang F, Watada H, Nicolucci A

Treatment Patterns and Associated Factors in 13,379 Patients with Type 2 Diabetes Initiating a Second-Line Therapy: The DISCOVER Study

Nicolucci A, Arya N, Charbonnel B, Cid J, Fenici P, Gomes MB, Hammar N, Kamal S, Khunti K, Kosiboro M, Shestakova MV, Shimomura I, Tang F, Watada H, Pocock S

ORAL PRESENTATION

Global Prevalence of Type 2 Diabetes Complications in 14,391 Patients Initiating Second-Line Therapy: The DISCOVER Study

Kosiboro M, Arya N, Cid J, Fenici P, Gomes MB, Hammar N, Kamal S, Nicolucci A, Pocock S, Rathmann W, Shestakova MV, Shimomura I, Tang F, Watada H, Khunti K

American Headache Society 59TH Annual Scientific Meeting

Jun. 8-11, 2017; Boston, MA, USA

POSTERS

Development and Psychometric Validation of the Migraine Functional Impact Questionnaire (MFIQ): A New Instrument Measuring the Impact of Migraine on Physical, Social, and Emotional Functioning

Shaffer S, Mannix S, Kawata AK, Thach AV, Desai P, Buse DC, Bayliss M, Sapra S, Mikol DD, Hareendran A

The Impact of Migraine on Physical Functioning in Adults with Chronic and Episodic Migraine

Kawata AK, Hareendran A, Shaffer S, Mannix S, Sapra S, Desai P, Ortmeier BG, Lipton RB, Dodick DW, Stewart WF

International Congress of Parkinson's Disease and Movement Disorders

Jun. 4-8, 2017; Vancouver, BC, Canada

POSTER

Development of a Clinician-Reported Screening Tool to Identify Patients with Parkinson's Disease Inadequately Controlled on Oral Medications

Antonini A, Schmidt P, Odin P, Kleinman L, Skalicky AM, Sail K, Jalundhwala YJ, Zamudio J, Onuk K, Marshall T, Fernandez H

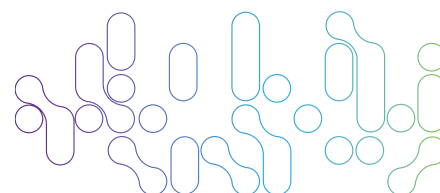
ASCO 2017

Jun. 2-6, 2017; Chicago, IL, USA

POSTER

Patient-Reported Outcomes and Quality of Life in ALTA: The Randomized Phase 2 Study of Brigatinib (BRG) in Advanced ALK+ Non-Small Cell Lung Cancer (NSCLC)

Langer CJ, Huang H, Huang J, Kerstein D, Reichmann W, Speck RM, Lenderking WR



Recent Publications

Ames NJ, Powers JH, Ranucci A, Gartrell K, Yang L, VanRaden M, **Leidy NK**, Wallen GR. **A Systematic Approach for Studying the Signs and Symptoms of Fever in Adult Patients: The Fever Assessment Tool (FAST).** *Health Qual Life Outcomes*. 2017 Apr 27;15(1):84. doi: 10.1186/s12955-017-0644-6.

Aoudia Y, **Kongnakorn T**, **Merinopoulou E**, Said Bettayeb M, Ahmed Kherraf S. **Cost-Effectiveness of Apixaban for Stroke Prevention in Patients with Atrial Fibrillation in Algeria.** *JHEOR*. 2017;5(1):39-54.

Benedict Á, **Ambavane A**, Tarhini A. **Comprehensive Reporting in Cost-Effectiveness Modeling.** *J Clin Oncol*. 2017 Sep 10;35(26):3085-3086. doi: 10.1200/JCO.2017.73.6355. Epub 2017 Jul 17.

Benjamin K, **Vernon MK**, Patrick DL, Perfetto E, Nestler-Parr S, Burke L. **Patient-Reported Outcome and Observer-Reported Outcome Assessment in Rare Disease Clinical Trials: An ISPOR COA Emerging Good Practices Task Force Report.** *Value Health*. 2017 Jul - Aug;20(7):838-855. doi: 10.1016/j.jval.2017.05.015.

Blieden M, Gandra SR, Cheng LI, Szatkowski A, Toth PP. **Differences in Utility Elicitation Methods in Cardiovascular Disease: A Systematic Review.** *J Med Econ*. 2017 Sep 12:1-23. doi: 10.1080/13696998.2017.1379410. [Epub ahead of print]

Caro JJ, **Moller J**. **Adding Events to a Markov Model Using DICE Simulation.** *Med Decis Making*. 2017 Jul 1:272989X17715636. doi: 10.1177/0272989X17715636. [Epub ahead of print]

Ciomek K, Kadzinski M, **Tervonen T**. **Heuristics for Prioritizing Pair-Wise Elicitation Questions with Additive Multi-Attribute Value Models.** *Omega (Westport)*. [In Press]

Ciomek K, Kadzinski M, **Tervonen T**. **Heuristics for Selecting Pair-Wise Elicitation Questions in Multiple Criteria Choice Problems.** *Eur J Oper Res*. [In Press]

Crins MH, Terwee CB, Klausch T, Smits N, de Vet HC, Westhovens R, Cella D, Cook KF, **Revicki DA**, van Leeuwen J, Boers M, Dekker J, Roorda LD. **The Dutch-Flemish PROMIS Physical Function Item Bank Exhibited Strong Psychometric Properties in Patients with Chronic Pain.** *J Clin Epidemiol*. 2017 Jul; 87:47-58. doi: 10.1016/j.jclinepi.2017.03.011. Epub 2017 Mar 28.

Cunningham NR, Kashikar-Zuck S, Mara C, Goldschneider KR, **Revicki DA**, Dampier C, Sherry DD, Crosby L, Carle A, Cook KF, Morgan EM. **Development and Validation of the Self-Reported PROMIS Pediatric Pain Behavior Item Bank and Short Form Scale.** *Pain*. 2017 Jul;158(7):1323-1331. doi: 10.1097/j.pain.0000000000000914.

Deitelzweig S, Farmer C, Luo X, Vo L, Li X, Hamilton M, Horblyuk R, **Ashaye A**. **Risk of Major Bleeding in Patients w/ Non-Valvular Atrial Fibrillation Treated w/ Oral Anticoagulants: A Systematic Review of Real-World Observational Studies.** *Curr Med Res Opin*. 2017 Sep;33(9):1583-1594. doi: 10.1080/03007995.2017.1347090. Epub 2017 Jul]

Desai VC, Ferrand Y, Cavanaugh TM, Kelton CM, **Caro JJ**, Goebel J, Heaton PC. **Comparative Effectiveness of Tacrolimus-Based Steroid Sparing versus Steroid Maintenance Regimens in Kidney Transplantation: Results from Discrete Event Simulation.** *Med Decis Making*. 2017 Oct;37(7):827-843. doi: 10.1177/0272989X17700879. Epub 2017 Apr 6.

Du M, Chase M, **Oguz M**, Davies G. **State Transition Model: Vorapaxar Added to Standard Antiplatelet Therapy to Prevent Thrombosis Post Myocardial Infarction or Peripheral Artery Disease.** *Curr Med Res Opin*. 2017 Sep;33(9):1535-1543. doi: 10.1080/03007995.2017.1301902. Epub 2017 Mar 12.

Faivre S, Niccoli P, Castellano D, Valle JW, Hammel P, Raoul JL, Vinik A, Van Cutsem E, Bang YJ, Lee SH, Borbath I, Lombard-Bohas C, Metrakos P, Smith D, Chen JS, Ruszniewski P, Seitz JF, Patyna S, Lu DR, **Ishak KJ**, Raymond E. **Sunitinib in Pancreatic Neuroendocrine Tumors: Updated Progression-Free Survival and Final Overall Survival from a Phase III Randomized Study.** *Ann Oncol*. 2017 Feb 1;28(2):339-343. doi: 10.1093/annonc/mdw561.

Gallone G, Haerty W, Disanto G, Ramagopalan SV, Ponting CP, Berlanga-Taylor AJ. **Identification of Genetic Variants Affecting Vitamin D Receptor Binding and Associations with Autoimmune Disease.** *Hum Mol Genet*. 2017 Jun 1;26(11):2164-2176. doi: 10.1093/hmg/ddx092.

Ganz ML, Tawah AF, **Guo S**, Chitnis AS, Silies H, Schäuble B, Jovalekic A, Foster NL. **The Impact of β -Amyloid Positron Emission Tomography on the Diagnostic and Treatment Decisions of Dementia Experts.** *Neurodegener Dis Manag*. 2017 Apr;7(2):107-117. doi: 10.2217/nmt-2016-0059. Epub 2017 Apr 26.

Gelhorn HL, **Roberts LJ**, Khandelwal N, **Revicki DA**, DeRogatis LR, Dobs A, Hepp Z, Miller MG. **Psychometric Evaluation of the Hypogonadism Impact of Symptoms Questionnaire Short Form (HIS-Q-SF).** *J Sex Med*. 2017 Aug;14(8):1046-1058. doi: 10.1016/j.jsxm.2017.05.013.

Gries KS, Regier DA, Ramsey SD, Patrick DL. **Utility Estimates of Disease-Specific Health States in Prostate Cancer from Three Different Perspectives.** *Appl Health Econ Health Policy*. 2017 Jun;15(3):375-384. doi: 10.1007/s40258-016-0282-x.

Gu Y, **Nordstrom BL**. **The Risk of Malignancy among Biologic-Naïve Pediatric Psoriasis Patients: A Retrospective Cohort Study in a US Claims Database.** *J Am Acad Dermatol*. 2017 Aug;77(2):293-301.e1. doi: 10.1016/j.jaad.2017.03.044. Epub 2017 Jun 13.

Hanner J, Cella D, Feeny D, Fischhoff B, Hays RD, Hess R, Pilkonis PA, **Revicki D**, Roberts M, Tsevat J, Yu L. **Selection of Key Health Domains from PROMIS® for a Generic Preference-Based Scoring System.** *Qual Life Res*. 2017 Aug 19. doi: 10.1007/s11136-017-1686-2. [Epub ahead of print]

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Evidera Welcomes

Dr. Debra Schaumberg as Vice President of Scientific Affairs for Real-World Evidence

Evidera is pleased to announce that Debra Schaumberg, ScD, OD, MPH, FAAO – an internationally recognized expert in epidemiology and ophthalmology – has joined Evidera as Vice President of Scientific Affairs for Real-World Evidence (RWE). Dr. Schaumberg will work with stakeholders in industry and academia, as well as across the Evidera organization, to contribute to the conceptualization, delivery and commercialization of new and emerging RWE solutions.

Dr. Schaumberg has more than 20 years of experience designing and leading large, high-caliber research studies. She is distinguished for her innovation, creation of rigorous and flexible study methodologies, proactive integration of biomarkers and genetics, and generation of high-quality data leading to hundreds of scientific publications, lectures, and scientific presentations. She has also made seminal contributions to the understanding of eye diseases, including groundbreaking work on dry eye disease, as well as age-related macular degeneration, cataract, and diabetic retinopathy.



Dr. Schaumberg served for nearly 20 years on the faculty at Harvard Medical School and the Harvard School of Public Health. Following Harvard, she was Professor of Ophthalmology and Visual Sciences at the University of Utah School of Medicine. She continues to serve as an adjunct professor at both institutions. Prior to joining Evidera, Dr. Schaumberg served as Global Medical Director for Ophthalmics, leading the medical launch strategy for Xiidra®, and then as Head of Medical Evidence at Shire, developing and leading the RWE strategy for the medical affairs organization across all therapeutic areas.

Dr. Schaumberg received her doctor of science degree from the Harvard School of Public Health, previously completing a master's in public health at Johns Hopkins, research fellowship at the Johns Hopkins School of Medicine, optometry residency at the Chicago VA Medical Center, and a doctor of optometry, summa cum laude, from the Illinois College of Optometry. She is the recipient of numerous awards, including the international Claes Dohlman Award from the Tear Film and Ocular Surface Society for her pivotal work on dry eye disease. She has been chosen as the inaugural recipient of the Women's Eye Health Ilene K. Gipson Award for her major contributions in advancing the role of gender in eye disease. She is an elected fellow of both the American Academy of Optometry and the American College of Epidemiology.

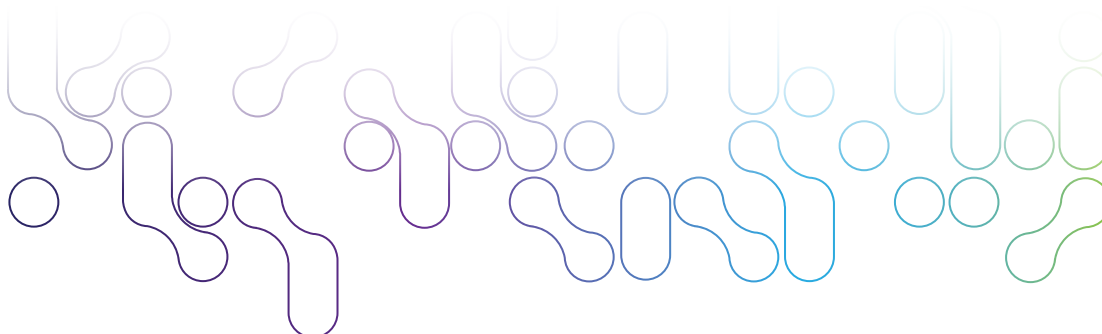
Dr. Ray Gani Joins Evidera's Modeling and Simulation Team as a Senior Research Scientist

Evidera is pleased to welcome Ray Gani, PhD, as a Senior Research Scientist with our Modeling and Simulation team. Dr. Gani has over 17 years' of experience in health economics and is responsible for leading health economic projects, principally focused on developing decision-analytic models for use during pricing and reimbursement negotiations. These models range from complex health technology assessment (HTA) models suitable for NICE, CADTH and PBAC, to simple budget impact models for use during formulary discussions. Dr. Gani also develops early-stage models for strategic planning and gap analysis, conducts burden of illness studies for HTA assessments, and supports RCT and observational study design so appropriate data is collected for economic analyses. His experience covers Europe, Australia, Asia, and North America, and several therapy areas including oncology, multiple sclerosis, respiratory disease, infectious disease, cardiovascular disease, and diabetes.



Dr. Gani was previously an associate principal at QuintilesIMS Global Consulting, specializing in health economics. He has also held roles as European HEOR director at Astellas, UK HEOR team leader at Boehringer Ingelheim, technical lead for economic evaluation at Heron Evidence Development, and head of quantitative risk assessment at the Health Protection Agency (now Public Health England).

Dr. Gani has presented studies at international conferences and authored publications for *Nature*, *Emerging Infectious Diseases*, *Journal of Economics*, *Pharmacoeconomics*, *Heart*, and *Value in Health*. Dr. Gani has a PhD in economic modeling from the University of Strathclyde, an MSc in mathematical modeling from the University College London, and a BSc (Hons) in mathematics from the University of Leicester.





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