

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

Marissa Mihos, MPH  
Research Associate, Real-World Evidence, Evidera

Daryl Spinner, PhD, MBA  
Managing Director, Real-World Value and Strategy, Real-World Evidence, Evidera

Moira Ringo, PhD, MBA  
Senior Consultant, Real-World Evidence, Evidera

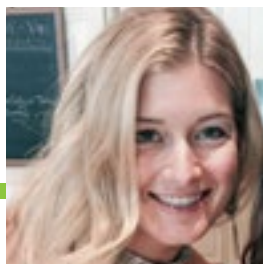
Eric Faulkner, MPH  
Vice President, Real-World Value and Strategy and Executive Director, Center for Precision and Transformative Technology Solutions, Evidera

## 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,<sup>1</sup> 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).<sup>2</sup> 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.<sup>3</sup> 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



Moira 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 21<sup>ST</sup> 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.<sup>4</sup> 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.<sup>9</sup> 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 21<sup>ST</sup> Century Cures Act**

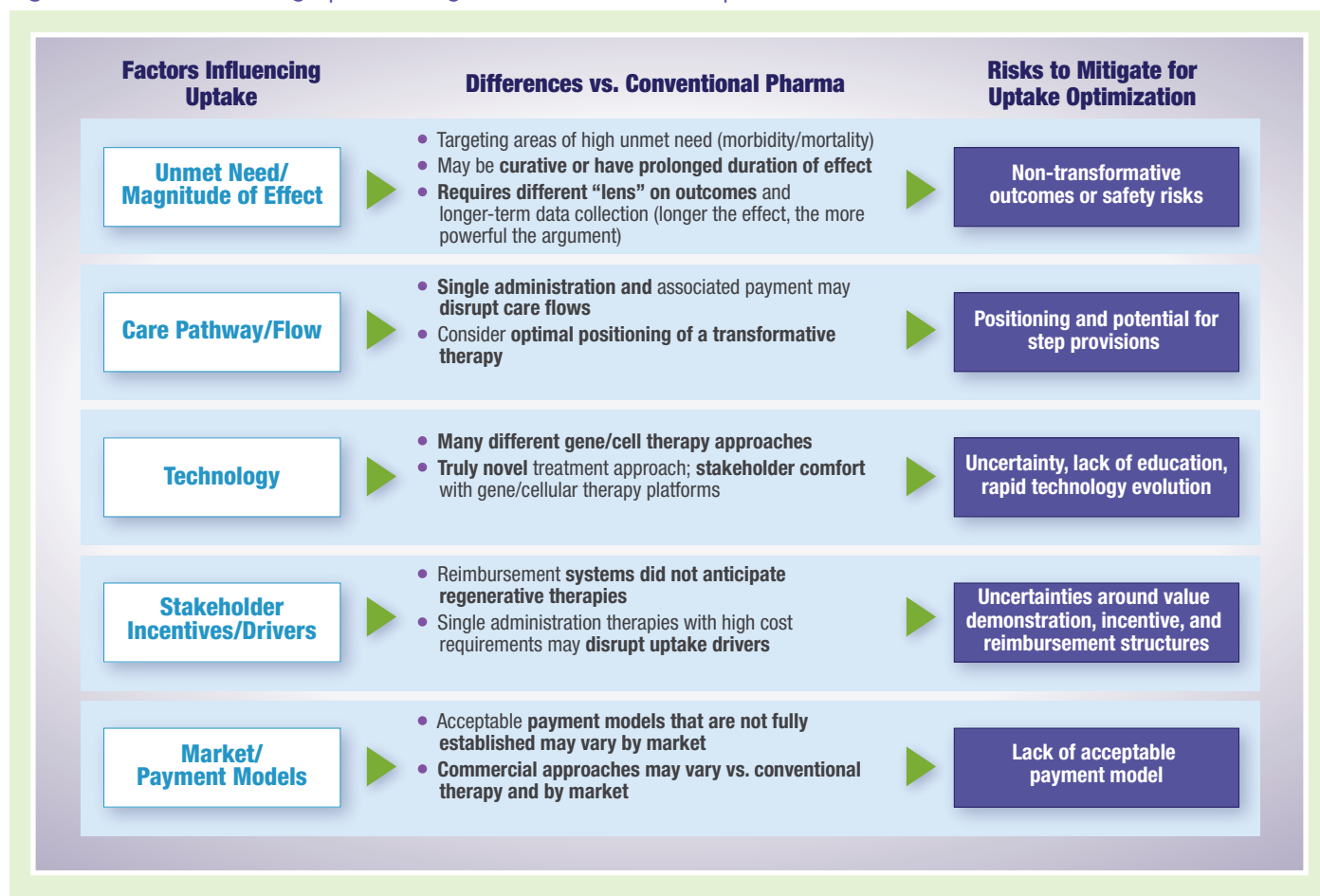
<b>Serious or Life Threatening Disease<sup>5</sup></b>	Disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible if it is persistent or recurrent. 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.
<b>Preliminary Clinical Evidence</b>	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. <sup>6-8</sup>
<b>Unmet Need</b>	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). <sup>7</sup>

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,<sup>10</sup> 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.<sup>11</sup> 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

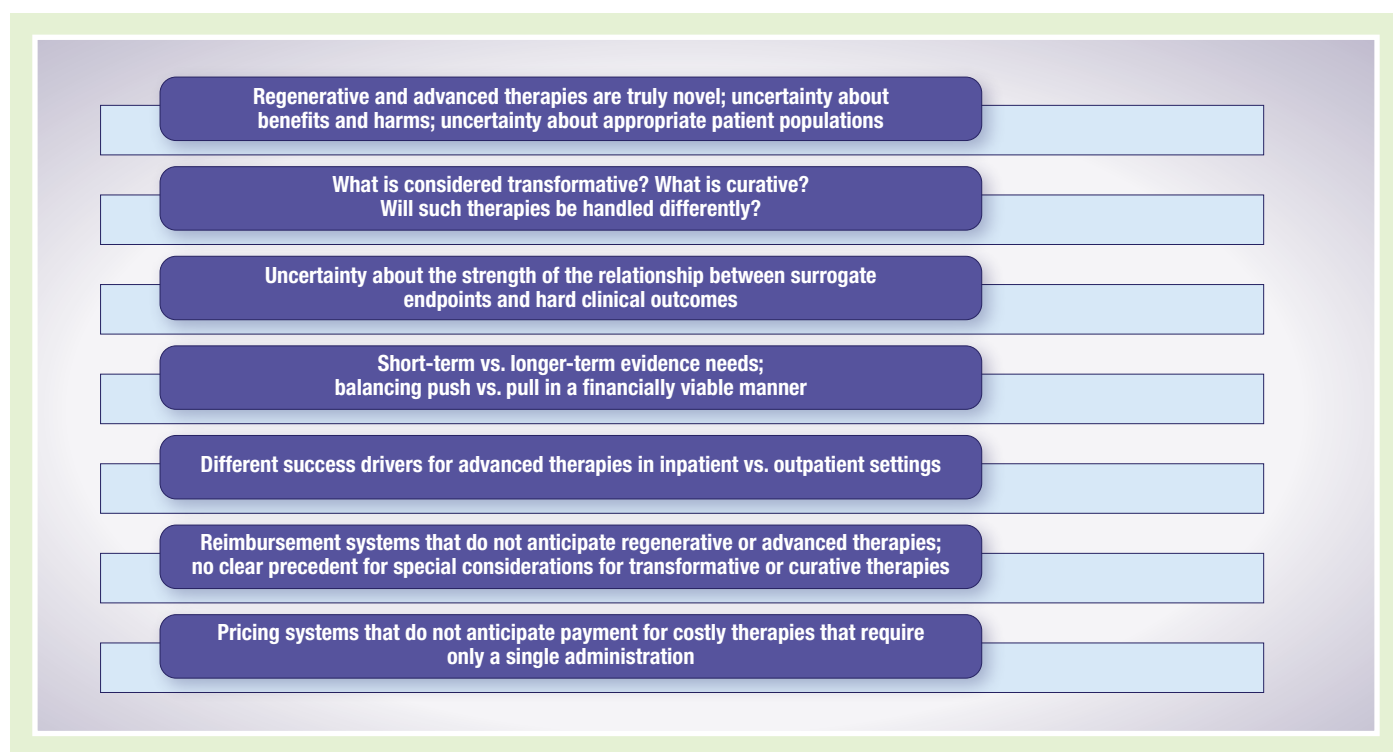
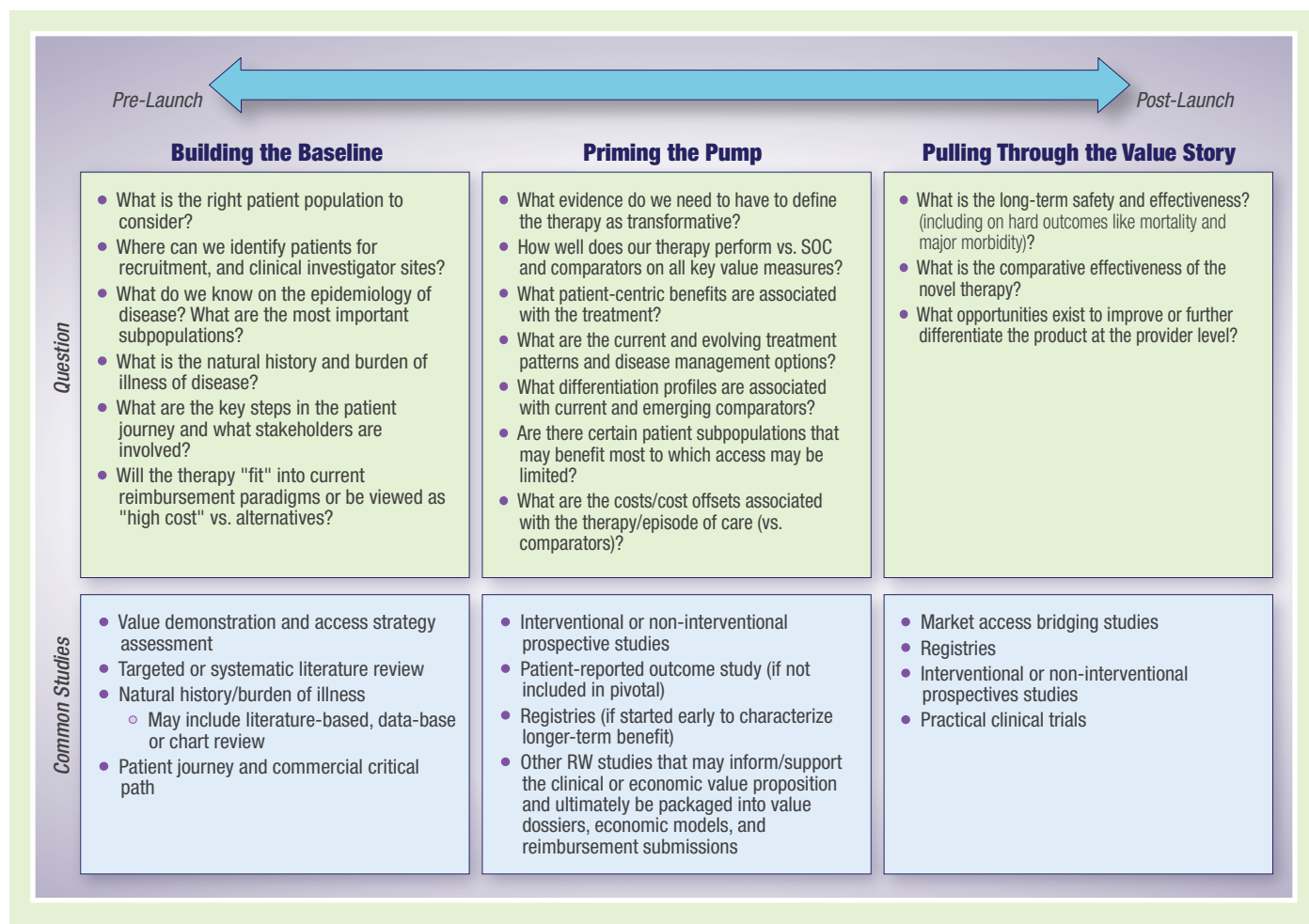


Figure 4. Aligning Regenerative Medicine Evidence Questions with RWE Approaches



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.<sup>26, 27</sup> 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
<b>Retrospective data analyses (linked or unlinked health chart and/or insurance claims review)</b>	<ul style="list-style-type: none"> <li>• Generate epidemiological, clinical, humanistic, and health economic evidence to support burden of illness/unmet need addressed and value of therapy (B)</li> <li>• Define patient journey, diagnostic criteria, subpopulations, key outcomes, and SOC/comparators (B)</li> <li>• Define current and historical treatment landscape (B)</li> <li>• Identify sites with high volumes of patients, and potential investigators for pivotal studies, observational studies, and registries (P)</li> <li>• 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)</li> </ul>	<ul style="list-style-type: none"> <li>• Characterize and quantify how the therapy addresses disease burden and fills existing unmet need</li> <li>• Define existing treatments, best placement targeting therapy, and where patients may fall through the cracks</li> <li>• Define your transformative or differentiation story</li> <li>• 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</li> <li>• Establish baseline disease outcomes in SOC and/or comparator-treated control patients (especially when blinding and/or randomization not possible, or patients are rare)</li> <li>• Define the resource use associated with alternatives to help make a case for novel coding/payment levels (as appropriate)</li> </ul>
<b>Observational data collection in parallel to pivotal study/ RCT</b>	<ul style="list-style-type: none"> <li>• 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)</li> </ul>	<ul style="list-style-type: none"> <li>• Anticipate and address subpopulation data effects that may be relevant to HTA and payer authorities, but cannot be included in pivotal studies</li> <li>• 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.</li> </ul>
<b>Prospective observational (cohort) studies</b>	<ul style="list-style-type: none"> <li>• Define patient journey, potentially relevant patient subpopulations, and SOC/comparators (B)</li> <li>• Monitor evolving treatment landscape (P)</li> <li>• Tracking safety and effectiveness, before, during, and after treatment (P, V)</li> <li>• Monitor treated patients for potential subpopulations who benefit more from treatment, and opportunities for continued product differentiation (P, V)</li> </ul>	<ul style="list-style-type: none"> <li>• Demonstrate real-world durability of treatment effect, and safety post-launch</li> <li>• 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</li> <li>• Monitor for opportunities to improve product or health benefit/ effectiveness and/or safety in the real-world</li> </ul>
<b>Registry studies</b>	<ul style="list-style-type: none"> <li>• Capture and track long-term outcomes, safety/effectiveness required by regulators, continued value demonstration for payers, and alternative payment models (V)</li> <li>• Monitor treated patients for potential subpopulations who benefit more from treatment, and opportunities for continued product differentiation (V)</li> </ul>	<ul style="list-style-type: none"> <li>• Demonstrate real-world durability of treatment effect and safety post-launch to support market access as launch sequence progresses</li> <li>• Demonstrate ongoing product value to support global access through prolonged duration of therapeutic effect and safety measures</li> <li>• Monitor real-world use and treatment patterns for other patient populations/follow-on indications</li> <li>• Satisfy regulator requirement for prolonged and ongoing post-marketing safety data with most transformative therapies</li> <li>• Capture key ongoing outcomes to support alternative pricing models/outcomes-based payment increasingly required for costly, transformative therapies<sup>11</sup></li> </ul>

- 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
<b>Building the Baseline</b>	<ul style="list-style-type: none"> <li>● Defining who the target patient is and how they get there, especially in indications with “softer” diagnostic criteria</li> <li>● Defining BOI, especially in rarer indications and those with uncertain diagnostic criteria</li> </ul>	<ul style="list-style-type: none"> <li>● Demonstrate regenerative medicine comparative efficacy with complete characterization of pre-treated and SOC-treated patients</li> <li>● Generate natural history data to establish course of disease</li> <li>● Demonstrate lack of effective treatment options</li> </ul>	<p><b>Successes:</b> 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 options<sup>12</sup></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 baseline<sup>12-17</sup></p>
<b>Priming the Pump</b>	<ul style="list-style-type: none"> <li>● Identifying where to find sufficient target patients to reach trial recruitment goals and adequate powering</li> <li>● Rapidly recruiting target patients for trial enrollment</li> </ul>	<ul style="list-style-type: none"> <li>● Retrospective data analysis to identify relevant subgroups</li> </ul>	<p><b>Challenges:</b> 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<sup>18,19</sup></p>
<b>Pulling Through the Value Story</b>	<ul style="list-style-type: none"> <li>● Avoiding evidentiary uncertainty in demonstrating “transformative” product value</li> <li>● Adequately capturing critical measures of value to align with anticipated product pricing</li> </ul>	<ul style="list-style-type: none"> <li>● Characterize implications of surrogate endpoints to help establish SOC baseline</li> <li>● Run indirect treatment comparisons alongside pivotal studies</li> <li>● Anticipate need for retrospective analyses of trial data to identify patient subpopulations</li> <li>● Real-world, post-market, follow-up plan for safety and effectiveness coupled with a risk sharing strategy to help enable uptake</li> <li>● Natural history data to establish course of disease</li> </ul>	<p><b>Successes:</b> Tisagenleucel (CAR-T therapy) single-arm pivotal study in ALL leveraged RWE approaches to demonstrate transformative benefit vs. most-relevant comparator</p> <p><b>Challenges:</b> 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 study<sup>20</sup></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 months<sup>21</sup></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<sup>22,23</sup></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

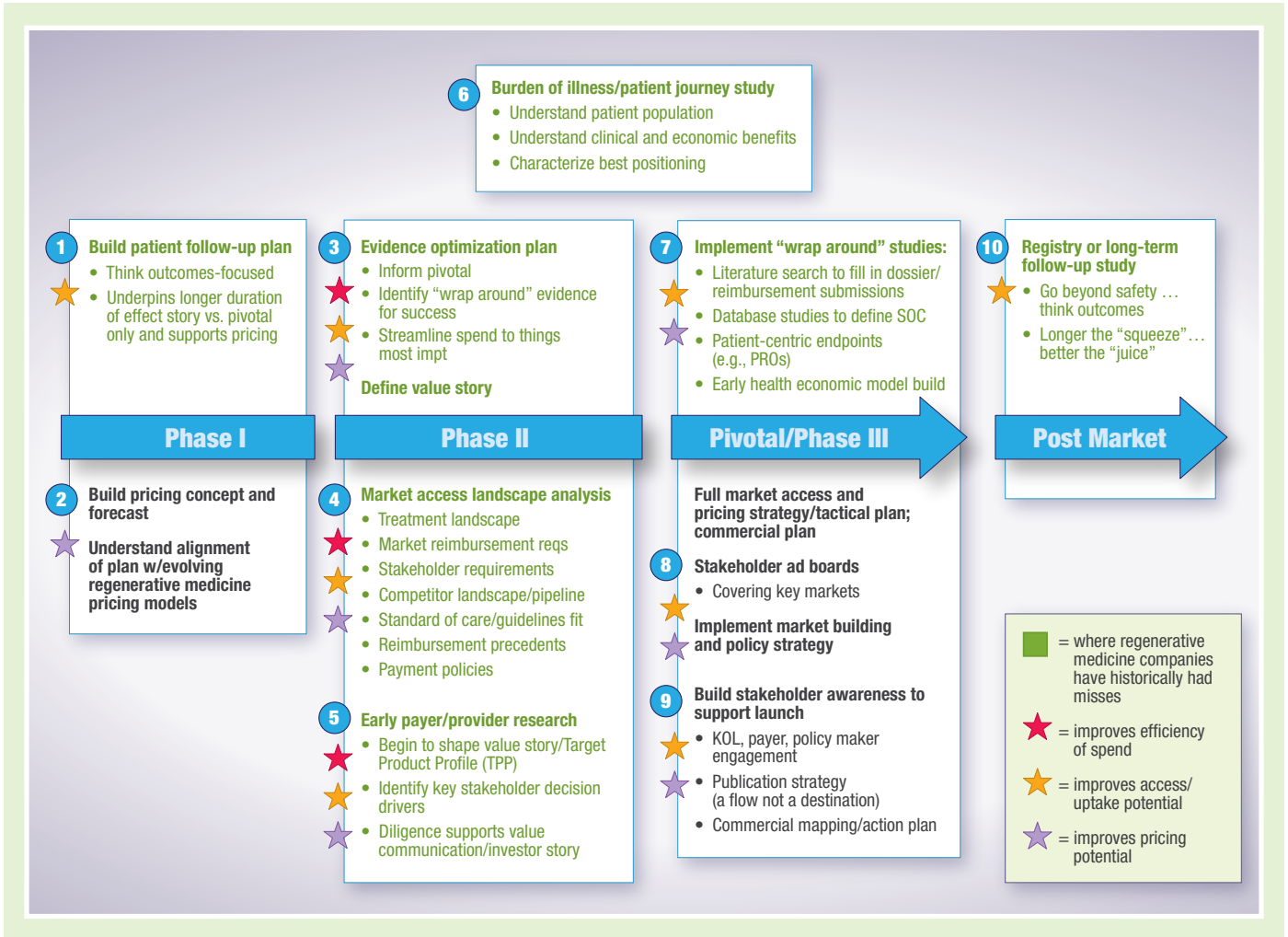


most important aspects (cited by 60-80% of respondents) of value demonstration in a recent payer survey lead by Faulkner and colleagues.<sup>28</sup> While simple in concept, the devil is in the details in terms of appropriately addressing these value dimensions in a manner that is aligned for the value 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

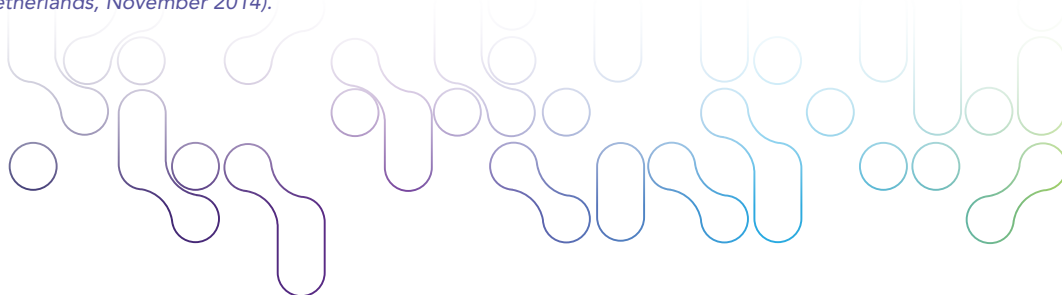
opportunities for building a value case acceptable to providers, hospital networks, health technology assessors, and payers will help ensure that their products are sufficiently differentiated to realize the promise that these transformative technologies have to offer the future of healthcare delivery.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

For more information, please contact [Marissa.Mihos@evidera.com](mailto:Marissa.Mihos@evidera.com), [Daryl.Spinner@evidera.com](mailto:Daryl.Spinner@evidera.com), [Moira.Ringo@evidera.com](mailto:Moira.Ringo@evidera.com), or [Eric.Faulkner@evidera.com](mailto:Eric.Faulkner@evidera.com).

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, 17<sup>th</sup> Annual European Congress, Amsterdam, Netherlands, November 2014).



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