



Concise Review: The High Cost of High Tech Medicine: Planning Ahead for Market Access

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ABSTRACT

Cellular therapies and other regenerative medicines are emerging as potentially transformative additions to modern medicine, but likely at a staggering financial cost. Public health care systems' budgets are already strained by growing and aging populations, and many private insurer's budgets are equally stretched. The current systems that most payers employ to manage their cash flow are not structured to absorb a sudden onslaught of very expensive prescriptions for a large portion of their covered population. Despite this, developers of new regenerative medicines tend to focus on the demands of regulators, not payers, in order to be compliant throughout the clinical trials phases, and to develop a product that ultimately will be approvable. It is not advisable to assume that an approved product will automatically become a reimbursed product, as examples from current practice in hematopoietic stem cell transplantation in the U.S. demonstrate; similarly, in Europe numerous Advanced-therapy Medicinal Products achieved market authorization but failed to secure reimbursement (e.g., Glybera, Provenge, ChondroCelect, MACI). There are however strategies and approaches that developers can employ throughout clinical development, in order to generate clinical and health economic data which will be necessary to demonstrate the value proposition of the new product and help ensure market access for patients; furthermore, performance based managed entry agreements coupled with post-launch evidence generation can help overcome challenges around product uncertainty at launch and reduce market access delays. *STEM CELLS TRANSLATIONAL MEDICINE* 2017;6:1723–1729

SIGNIFICANCE STATEMENT

The development of cellular therapies faces a series of regulatory obstacles. Often overlooked will be barriers to utilization based upon reimbursement issues, practice guidelines, and payer contract restrictions. The authors provide guidance for early planning of reimbursement strategies to be performed by the cellular therapy biotechnology industry to assure successful launches within the U.S. multi-payer as well as the European Union members single-payer systems.

INTRODUCTION

Cell therapies have traditionally been developed in a limited number of countries, for specific clinical uses, with a narrow market niche in mind. The singular goal of the companies behind development of these technologies has been achieving market access via regulatory approval. However, in a world of stagnant healthcare budgets and increased deliberation over any new product's value proposition, it is critical to take a macroeconomic view early in cell therapy product development to ensure broad market access, long-term market viability, and the possible opportunity for global implementation for new “high tech, high cost” products. This article is written for those who are developing new cell, gene, and tissue therapies, with a goal of achieving regulatory

approval and payer coverage. While reimbursement has traditionally been considered as an issue for consideration toward the end of clinical development, we suggest multiple approaches to address these concepts early on and throughout clinical development.

The aging population in multiple countries is directly linked to increasing health cost expenditures. There have been many projections showing the cost of health care has been outstripping the gross domestic product within the U.S. The cost of cancer care, including the cost of relevant pharmaceuticals and therapies, is projected to consume a disproportionate percentage of U.S. health dollars [1, 2]. Over the past 20 years, there have been multiple administrative restrictions placed on high cost therapies, aimed at limiting access and utilization, despite the innovative therapies' potential or

proven clinical and societal benefits. Many types of cancers are targets for cellular therapies in development, and while these therapies are potentially life-changing and life-saving for individuals, they are potentially damaging to national health budgets [3, 4].

Traditional medical approaches often use pharmaceuticals or surgical techniques to stabilize, not reverse, clinical situations. The cellular therapy and emerging regenerative medicine fields hold promise that cells can be used to overcome damage caused by injury or disease to specific tissue and organs, possibly even offering some curative outcomes. Recognizing that the cellular therapy field is emerging, particularly around the launch of commercial prescription products, and the potential targets of regenerative medicine are vast, it is critical that both regulatory hurdles and reimbursement concepts are addressed early in the new therapies' development programs. The scope of a products' clinical trials must evolve in order to define and refine the understanding of the product's optimal patient and broaden the use across different patient types. This approach will help ensure that new cell therapy products in development can be approvable by regulators, financially acceptable to payers, and accessible to the patients who are most likely to benefit. Within that consideration, it is also critical that drug development be targeted not just for a single country in mind, but also with an understanding of barriers that exist when therapeutics are developed across multiple countries and multiple payer systems.

LESSONS FROM HEMATOPOIETIC STEM CELL TRANSPLANTATION—AN INSTRUCTIVE U.S. EXAMPLE

In the U.S., there are extensive reimbursement challenges for cellular therapies on the immediate horizon for individual biotechnology and pharmaceutical companies. One can use the stem cell transplant experience as a model for consideration if cellular therapies are to be used in a broad spectrum of acute and chronic medical disorders. Hematopoietic stem cell transplantation (HSCT) is the only curative therapy for many inherited or acquired malignant and nonmalignant disorders. It has been recognized as a standard of care and there have been dramatic improvements over the past two decades that have enhanced its efficacy with improvements in patient overall survival [5]. HSCT is often reimbursed with global case rates, which can be classified among the emerging "bundled payment" models that are often advocated for by supporters of health care reform. (For background on terminology, see review by LeMaistre and Farnia, which extensively discussed the language of healthcare reimbursement in the U.S. today [6]. HSCT is performed at a limited number of facilities with specialized capabilities, a system which is reinforced by payers' development of quality and value-based "centers of excellence" networks. Facilities performing HSCT are mandated to report patient outcomes to a central, federally-contracted registry for purposes of public transparency. Each center's one-year risk-adjusted outcomes are currently publicly available for allogeneic HSCT procedures within the Stem Cell Therapeutic Outcomes Database. Due to the clinically specialized and resource-intensive nature of HSCT, the transplant community has had to develop a partnership with payers. Over 20 years ago, the Blue Cross demonstration project provided funding for autologous stem cell transplantation for breast cancer and for multiple myeloma patients, but in context of Phase III randomized trials and with a predefined reimbursement rate. Thus, this

partnership with payers was forged out of necessity for both sides, but has continued collaboratively with practitioners to define standards and expected value outcomes.

Despite this partnership, HSCT is not immune to the scrutiny associated with growing costs. In a recent report by the Milliman Group, it was identified that the average estimated billed charges per transplant were \$378,000 for autologous transplantation and \$930,000 for allogeneic transplant (30 days pre- and 180 days post-), a period of time that covered the hospital stay and the immediately subsequent post-HSCT management [7]. In addition to the Milliman report, the Agency for Healthcare Research and Quality (AHRQ) identified HSCT as the procedure with the most rapidly increasing hospital inpatient costs and hospital stays over a 48-month period [8]. At an institutional level, HSCT was previously associated with high positive margins for which transplantation programs were often invited to grow. However, over the past decade, there has been a significant change in payer mix in the HSCT patient population, as it moved from a therapy that was routinely only offered to relatively young, otherwise healthy patients who likely had commercial, employer-based insurance coverage to a standard of care for more indications and more varied groups of patients. Now nearly 40% of the HSCT procedures performed in the U.S. are covered by nonemployer based, governmental payer coverage as determined by a recent survey sponsored by the National Marrow Donor Program. The cost of product procurement is an essential benefit to the transplant patient. The payer has responsibility of these costs, however, patient may still face a range of expenditures depending on what the individual patients' payer benefit package covers [9]. Additionally, coverage of the transplant procedure has evolved as a global case rate, which may or may not include donor search and acquisition, patient care in the hospital and out of the hospital, all within a defined time period [6, 9]. In some situations, there can be carve-outs for unique cell sources, such as umbilical cord blood or utilization of special pharmaceutical agents. For patients on dialysis, dialysis chronic care costs can be carved out of the global case rate, all requiring detailed and complicated pre-procedure scheduling and planning [10].

Although the actual stem cell transplant event—the infusion of the cells—occurs at a single point in time, reimbursement is increasingly focused on an *episode* of care [11]. As such, the cost of each item used or service provided within that episode of care is under financial scrutiny. This approach includes the actual cost of the individual transplant product, thus leading treating physicians and institutions to begin to consider cellular products based on cost of acquisition versus potential efficacy. Hospitals purchase donor cells from a registry in advance of the transplant infusion and these costs are nonrefundable. For instance, it is difficult to offer an adult patient with Medicare coverage a double cord transplant procedure, recognizing the cost of the acquisition of the cord products will consume nearly the entire designated MS-DRG (inpatient episode) payment. This can impact decisions regarding donor sources; most older adults in the trial will likely be offered haploidentical procedures if there is not a fully-matched adult donor available, based on the Medicare reimbursement for their care although there is a current Phase III randomized clinical transplant trial to compare efficacy of haploidentical transplant vs double cord blood in U.S. adults. Similarly, many costly pharmaceuticals are restricted from in-hospital use, where their cost might consume the inpatient bundle payment; these drugs are relegated to out-patient utilization where

reimbursement is provided by a daily Ambulatory Payment Classification (APC) coverage. APCs are assigned based on specific Current Procedural Technology codes and providers can typically assess associated reimbursement in advance [overview in Ref. 6].

In the U.S., most recent health care reform legislation, the Patient Protection and Affordable Care Act of 2010, the goals were to expand coverage and improve affordability [12]. One of these mechanisms is the health care insurance exchanges, where employers and individuals can purchase small group and individual policies. These policies are required to cover the 11 categories of essential health benefits based on a state-identified benchmark plan, but the regulatory standards which define the types of providers' health insurance companies are required to contract with, known as network adequacy standards, are not inclusive of all therapy types. This creates a situation in which many exchange plans do not allow access to the kinds of specialized hospitals and academic medical centers that perform HSCT or other cellular therapies. Additionally, the affordability of this coverage is decreasing with high-deductibles and significant premium rate increases for individual coverage.

When one considers the potential expansion of cellular therapies in the U.S., one also must consider the need for expansion of current payment models that will adapt to these new technologies. Particularly, what is at question is whether or not a cellular therapy can actually provide a lifetime cure. In the U.S., reimbursement is generally based upon "incident of care," as opposed to burden of disease reimbursement over a lifetime. If multiple therapies can be curative, and thus worthy of high price tags, one could begin to wonder as a society of how many lifetime curative payments an individual will be permitted. Previously, the state of Oregon made a decision that Medicaid beneficiaries were only allowed one transplant in their lifetime [13]. If a beneficiary had previously had a renal transplant and developed a treatment-related malignancy afterward, no second transplant was available. Similarly, before procedure and lifetime caps were restricted by the ACA, it was common to see patients with employer-based self-funded plans who would expend their benefits with one payer and necessarily migrate to another payer during the open enrollment period in order to reset the cap. We anticipate that we may see these kinds of "once per lifetime/year/decade" restrictions placed more frequently as therapeutic costs are higher. Alternatively, we must also consider whether or not a pharmaceutical or biotechnology company that is offering a curative therapy will share the financial risk if the patient does not have the optimal outcome that justified the price in the first place. Currently, the risk lies with the treating hospitals and the payers.

These examples teach us that even a cellular therapy product portfolio with decades of utilization and experience, still has limitations on utilization and access. It further shows that despite a product being unique, patient-directed, lifesaving and innovative, holes in coverage are common, and patients and families have increasing out-of-pocket expenditure [14]. Physician and hospital groups are being confronted with increasingly restrictive case rates around the cell therapy and thus, individual patient care recommendations can be heavily impacted by external financial issues.

In summary, a therapy's status as a preferred or standard-of-care treatment for certain illnesses does not mean it will be reimbursed without complications. Parties associated with new therapies need to understand the potential reimbursement hazards associated with planned site of care, coding structures, healthcare legislation, payer-driven utilization requirements and the types of payers associated with the patient population being treated.

MEANWHILE IN EUROPE

In Europe, challenges for cell therapy reimbursement are also broad and vary between countries and their regions [15]. It is readily recognized that there are significant variations in pricing and reimbursement frameworks amongst the five largest European Union (EU) countries (Germany, U.K., France, Spain, and Italy), that is, the Big5EU.

When one examines whether or not innovative therapies such as cellular therapies can be adopted, there are multiple considerations that must be taken by biotechnology and pharmaceutical companies seeking registration and reimbursement in Europe.

Across the Big5EU, private insurance does not provide significant advantage over public in terms of formulary inclusion of innovative therapies. Furthermore, and unlike the U.S., in these countries, healthcare expenditure is largely driven by public health insurance rather than private payers. Thus, for companies who are pursuing cell therapy adoption across Europe, efforts should be made to pursue public payer reimbursement and to account for public payer reimbursement requirements early in development.

The market authorization for a new medicine via the centralized route involves a series of scientific, clinical and quality reviews by the European Medicines Agency (EMA) [16]. Following market authorization, payers on a country-by-country basis undertake a review of the clinical evidence prior to conducting the economic review. Unlike the EMA where the focus of the clinical review is efficacy and safety, the clinical review undertaken by payers concentrates on assessing comparative effectiveness against an existing therapeutic alternative/best supportive care. The magnitude of the incremental clinical benefit identified is then used as a basis for the economic analysis, alongside cost considerations. As a final step before a patient can receive a new therapy, a decision to include that therapy on any one formulary is generally made at the local level and is subject to budget impact considerations and can change periodically with budget cycles.

Despite the many different administrative routes, the end target is to bring clinically- and cost-effective products to market, and to achieve this, there needs to be both regulatory approval as well as endorsement by health technology assessment bodies as well as other payer organizations at national, regional and local level within a given country.

To date, there are multiple examples where cellular therapies failed to secure reimbursement following market authorization due to insufficient comparative effectiveness data. Similar to the current shift in the U.S., the assessment of reimbursed pricing for innovative therapies in Europe has shifted toward value-based models. Demonstration of incremental benefit against existing therapeutic alternatives is the cornerstone to securing a premium price. Thus, a company should be prepared to provide supporting evidence at launch that demonstrates such benefits. This necessitates the generation of clinical and economic comparative data against the standard of care or best supportive care practices relevant to a given country. With this baseline acknowledgement, it is important also to recognize that there are additional factors that can influence governmental decisions on reimbursement in Europe, including the size of the target population, the disease burden and level of unmet need; as the size of the target patient population decreases and the level of unmet need increases, the willingness to pay increases. Similar considerations apply for therapies targeting end-of-life populations.

Some cell therapies make claims of long-term benefits in the absence of supporting long-term data obtained directly from

Table 1. Reimbursement-related concepts for each phase of clinical product development

Development phase	Key concept to consider	Source of information
Preclinical	Is there currently a well-defined disease or condition with treatments that are currently defined by codes and reimbursed?	Current market access and competitor landscape, as shown in payer policies, ICD-10 codes, and payment codes. Medicare National and Local Coverage Determinations and the Medicare Code Editor.
Early clinical	Do the safety results support moving to the next trial phase? Payers can deny coverage on the basis of inadequate patient safety.	Identify any products approved for use to treat the target condition but face challenges in payer acceptance due to safety concerns.
Phase IIa/IIb	Trial design issues (see Table 2) Are the reimbursement pathways clearly defined?	If no coding exists, start gap-analysis process. Identify appropriate medical society partner to understand coding process and timeline. New codes may take 1–3+ years to secure.
Phase III	What will your product's final label say?	Request payer input on pivotal trial design; ensure that endpoints and scales used to measure endpoints are payer-friendly. Review previous similar experiences (e.g., Dendreon)
Pre-Market	Payer negotiations based on phase 3 data	Price and coverage decisions; Results of therapy value assessment by various methods may impact contracted pricing.
Post-market	Contracts/price changes	Annual/ongoing pricing negotiations will require continuous data collection and analysis to justify coverage and payment level.

clinical trials. Whereas statistical regression methodologies do exist that enable manufacturers to conduct extrapolations based on short-term data, the acceptability of such approaches and derived modelled data across countries varies. In England specifically, there are clear health technology assessment guidelines issued by the National Institute for Health and Care Excellence (NICE) on how long-term claims can be substantiated through such approaches.

In certain cases, the lack of robust long-term data can be overcome by performance-based pricing agreements, for example, ChondroCelect, in Spain, where such an agreement was reached between healthcare providers and the manufacturer. In this case, if the product failed within the first year, there was 100% refund to the health care provider; the amount of the refund diminished over a 3-year period. (However, it should be noted that this agreement is no longer applicable as ChondroCelect was recently withdrawn from the European markets). Another example is the recent admission to the Italian reimbursement of Strimvelis at a price of 594,000 euros, Glaxo-SmithKline offers this one-time treatment for severe immunodeficiency stemming from a lack of adenosine deaminase (ADA-SCID) with a money-back guarantee for patients failing to sustain the curative benefit.

Finally, for cell therapy development in Europe, it is also important to account for the impact of the regulatory status on pricing, reimbursement and market access processes for example, unlike the EMA's "Advanced-therapy Medicinal Products" ATMP [17], minimally manipulated cell therapies, can bypass some of the national regulatory requirements and be assessed and determined for utilization at the hospital level only. As another example, if a medicinal therapy has secured compassionate use status in Germany, the manufacturer has to provide the treatment free of charge, while in the other four markets, a price can be individually set. In summary, it is critical to recognize that in the EU, despite centralization of the market authorization process, reimbursement is heavily fragmented across multiple countries and across regions of a given country. Early consideration of the individual markets are necessary for successful adoption.

In summary, although approval for new products must be obtained from the multi-country representative EMA panel, developers still most recognize that reimbursement frameworks differ

across individual European countries. Manufacturers need to engage with European payers prior to embarking on pivotal trials, so that payer evidence requirements can be met at launch and patients access and revenue generation can be secured without delay. As the recent withdrawal from the European markets of the majority of licensed ATMPs exemplifies (Glybera, ChondroCelect, MACI, and Provenge), securing market authorization is of little value if reimbursement cannot be secured because payer evidence requirements are not addressed or if utilization is so limited, that maintaining access to the unused product becomes impossible for the manufacturer. We anticipate that the forward-thinking approach of the EU SEED (Shaping European Early Dialogues for health technologies) program with its goal of initiating early dialogues between European health technology assessment agencies and those companies developing products, will create better harmonization toward directing more unified approaches to product development within the Big5EU.

DEVELOPING ACCESSIBLE CELL THERAPIES

Knowing these constraints, how then does an organization, whether it is a university research program or a global biotechnology company, employ a successful strategy toward developing commercial cell therapies? We offer a few suggestions for those seeking to serve all masters and pursue successful market adoption.

Prove Efficacy and Economically Viability at the Same Time

At the outset, it is important to recognize that the end goal of clinical development should be to develop effective medicines with acceptable risk/benefit profiles that physicians and other providers will utilize and prescribe, that patients will benefit from and, of course, that someone will pay for. Thus, one must understand not just what it takes for a product to be approved by regulatory agencies, used in the clinic, and accepted by payers, but also to understand *how* therapeutic products are reimbursed. The bulk of Regulatory submissions, payer negotiations, and marketing claims were traditionally based upon data generated in one or two Phase

Table 2. Trial design and potential impact on reimbursement

Trial aspect	Issues	Reimbursement impact
Inclusion/Exclusion	Is this patient population already well defined and covered by most major payers?	If no, then product will likely add to payer burden. Consider generating peer-reviewed data regarding the medical necessity for the treatment of the condition, and economic justification for a new approach.
Endpoints	Are the primary and secondary endpoints true measures of concepts that are meaningful to patients (QOL, QOLY), MDs (safety, PFS, OS), and payers (predictable costs, limited outlier)?	Payers will want to compare your results to current treatments' results. To do so, they will need to have the same or very similar endpoints.
Scales	Are the instruments or scales being used to quality an endpoint considered to be routine and accepted? For example, there are validated scales to measure QOL, and these are generally applicable across a wide variety of medical conditions.	Developers should use validated scales that are available in multiple languages. New, nonvalidated measures of clinical effect can be time consuming and distracting for those trying to evaluate a new treatment's effect.
Duration to endpoint	Sponsors may generally like to reach a primary endpoint as quickly as possible to minimize costs and accelerate decision-making about further clinical trials. The product must be tested long enough to show a sustained effect.	If the duration of effect is too short, payers may not cover without evidence of longer time of impact.
Comparator	Is the comparator used in the clinical trial truly the current standard of care? How much does it cost vs your expected initial cost? Will your product be associated with other directly related costs in the care episode (e.g., apheresis, biopsy, cell processing costs, final product preparation at clinical site)?	If comparator is realistic and the new product will be more expensive to the health care system, then you have a higher hurdle to prove substantial clinical improvements and/or improved quality of life.
Health economic measures	A trial's secondary endpoints should include measures relevant to the product's impact on financial factors for health care system and the patient. Length of stay in the hospital, increase or decrease in the use of concomitant medicines or medical services, and the ability to return to/begin work should all be considered	Payers will look to assess the value of a new treatment based on both clinical and economic impact. Evidence is needed to support coverage for the target patient population.

III trials. However for certain advanced therapies targeting indications of high disease burden and unmet need, clinical development programs can get accelerated approval and the routine phase III trials may be by-passed. Therefore, product developers must start addressing reimbursement considerations early in development. Several of the key issues to address by phase are described in Table 1, where key concepts for commercialization and information sources are outlined for all phases of clinical development.

At the time of applying for approval, sponsors must provide regulators with all of the data needed to assess a new therapy's clinical risk and benefit. Likewise, payers need to be given the relevant data necessary to evaluate the new product's medical necessity, its economic impact versus the impact of other treatment options on their overall budget, and anticipate what contract language will apply to the therapy. Furthermore, if a product is approved by regulators, and if payers opt to cover it, the product will launch into modern healthcare's vast pre-existing system of disease and procedural codes, which impact directly on a patient or clinic's ability to be reimbursed for the use of that product. In order to generate all of the data needed for regulators and payers, and to fit well within the existing system of codes, early on in development sponsors should assess their product's likely clinical setting for use (e.g., inpatient or outpatient), the competitive markets of other therapies, it's regulatory pathway, and the types of health economic data that payers will expect to see.

Plan Trials That Support the Desired Label

It is well understood that there are multiple steps in the clinical development pathway and it is beneficial and necessary for a company to identify the target patient population for which the

therapeutic will be applied. To that end, in the U.S., the FDA has guidelines on the development of a target product profile for submissions which act as an algorithm to simplify the complexity of the work that went into the pre-clinical and clinical development into identifying what the product label will claim [18]. This knowledge and approach is essential for a company to understand, as the approved product label is the sole basis for all marketing claims. Once the label is defined, individual practitioners may utilize a product outside of the label, but this runs the risk that payers can and will refuse reimbursement for that use. Companies developing cellular products will wish to have as broad a label as possible, but it is also recognized that individual payers can have language that will limit the situation or the individual patients for whom the product is indicated, and may also not provide coverage for as long a duration as is covered by the label. There are many examples where the label of the FDA-approved indication had significant restrictions. One could examine the coverage for the prostatic dendritic cell vaccine, Provenge, as a good example. While the labeled indication is quite straightforward, the health insurance policies for coverage are quite complex (e.g., see health benefits policy for Aetna) [19].

For some products, rather than assuming there will be a broad, patient application, it is best to understand which specific patients and which products will be covered. Will coverage for patients have restrictions based on age, gender, pre-existing comorbidities, previous treatments, as well as patients' individual policies? It is recognized that coverage for treatment may vary from payer to payer, from region to region, and based upon prior or concomitant therapies. Many new pharmaceuticals in the cancer world are being approved with a label for use only after the

patient has had two failed prior therapies. These concepts are summarized in Table 2.

Understand Your Markets and Their Reimbursement Requirements

Considering issues of market access should be done at the earliest stages of the product development decision making process. In other words, prior to embarking on initial clinical studies, the sponsor needs to understand the current market landscape for the product's target indication and target patient type, in terms of the products available, the reimbursement profiles of these products, the typical coverage policy of major payers, and the true "front lines" implementations of those policies.

Once the market access landscape for the given indication is understood, this information can be used to help define the economic criteria that the product must meet in order to be successful. These criteria may be as broad as defining the upper limit of the cost of manufacturing for each product, or the clinical outcome that is necessary to support a positive health economic profile. In the same way that existing clinical knowledge and norms are used to choose and set a clinical trial's primary endpoint, existing market access data should be used to set internal business development criteria as well as contribute to the clinical trials' secondary endpoints.

In order to address reimbursement concepts as one approaches a clinical trial, there should be attention at identifying the setting in which the product will be used, whether inpatient, outpatient, physician office, or within the home. Reimbursement can definitely vary based upon the setting in which the product is used. One must also identify the current treatments that are available for the individual specific indication as well as what may be the current language in regulatory restrictions on analogous products.

Another often overlooked issue is to understand the existing reimbursement diagnostic and treatment codes (ICD-9/10; CPT [6, 20, 21] their applicability to a new product and how billing and payment will flow through health care systems for individual indications. Coding is the numerical description of the care the patient received and the work involved in providing that care, and it allows for the health care provider's efforts to be rewarded appropriately [22]. If a new code is needed, the manufacturer will likely need to partner with a professional physician society or other provider group to seek the relevant codes. The processes to request new codes are very specific and can take 1–3 years to secure.

Health technology assessments can also be anticipated to be required by governmental agencies and private payers. They will be assessing the economic impact of the product on their budget, as well as taking a broad look at the impact of utilization of the product in health care. Specifically, they will look at cost of product, what other costs are generated, and does it actually change current treatment and lead to economic improvement. Thus, even after pivotal studies are performed and are positive, after approval of a regulatory agent, there still must be negotiation to obtain

coverage from numerous types of payers. There must be recognition that sometimes with new therapeutics, coverage can be limited to subsets of populations, limited number of doses while assessments are requested longitudinally. Initial coverage can sometimes be given with an expiration date if further supportive data do not mature and become available. Finally, in the world of payer negotiations, as seen in the U.S., individual therapies are often single items in complex contracts that are renegotiated every several years. Thus, as further information is gained, it must be expected that initial reimbursement approvals may not be maintained long term. While it is recognized that the burden is entirely upon the sponsor to drive a reimbursement development, other stakeholders can assist in achieving appropriate reimbursement. These other groups include patient advocacy groups, hospitals, physicians, and occasionally governmental agencies and individuals.

The standards for the scientific assessment and regulation of emerging therapies have proceeded toward global harmonization over the past several decades. However, health technology assessments, which evaluate a new product's value proposition for patients and payers, are as local as each region's health budget. However, there are efforts underway in the U.S. and EU to provide a pathway for parallel scientific and health technology assessment. The goal of such a parallel review is to provide sponsors with an early review of the evidence they will need to generate throughout clinical development in order to satisfy the requirements of regulators and multiple payers.

CONCLUSION

In this emerging field, evidence will guide the decisions by regulators and payers alike, and sponsors will do well to collect data that satisfies both groups' needs. Building in health economic measures to clinical data collection or conducting companion studies specifically on economic aspects of the clinical use of a product will ensure that throughout clinical development, data is generated to define the overall value proposition of the product for regulators, patients, providers, and payers.

AUTHOR CONTRIBUTIONS

D.D. and R.T.M.: conception and design, collection and/or assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript; S.F. and P.K.: collection and/or assembly of data, manuscript writing, final approval of manuscript.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

D.D. is CEO of a biotech start up, Partial owner of IP in biotech start up, and a consultant. R.M. is a consultant with Novartis, Inc. The other authors indicated no potential conflicts of interest.

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