Office of Health Economics Research

February 2019

Seminar Briefing 25

Early Experience with Health Technology Assessment of Gene Therapies in the United States: Pricing and Paying for Cures

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1. Introduction

The Institute for Clinical and Economic Review (ICER)[1] is an independent organisation founded in the US in 2006. Its remit is to evaluate the clinical and economic value of health care interventions – prescription drugs, diagnostic tests, and a range of others – and innovations in the delivery of care. ICER involves key stakeholders including patients, doctors, life science companies, private insurers, and the government to help ensure its research informs important policy decisions. Regional independent appraisal committees hold public hearings on each report. All reports are publicly available without charge.

One of ICER's core areas of activity is drug assessment reports that incorporate data on efficacy, economic value, and other elements of value important to patients and their families. The reports provide a "value-based price benchmark" meant to indicate drug pricing that encourages improved patient outcomes not just today, but over the longer term. Our reports also evaluate the potential short-term budget impact of new drugs to alert payers and policy makes in situations where short-term costs may strain health system budgets or threaten patient access. To avoid conflicts of interest, all ICER reports are produced with funding exclusively from non-profit foundations and other independent sources.

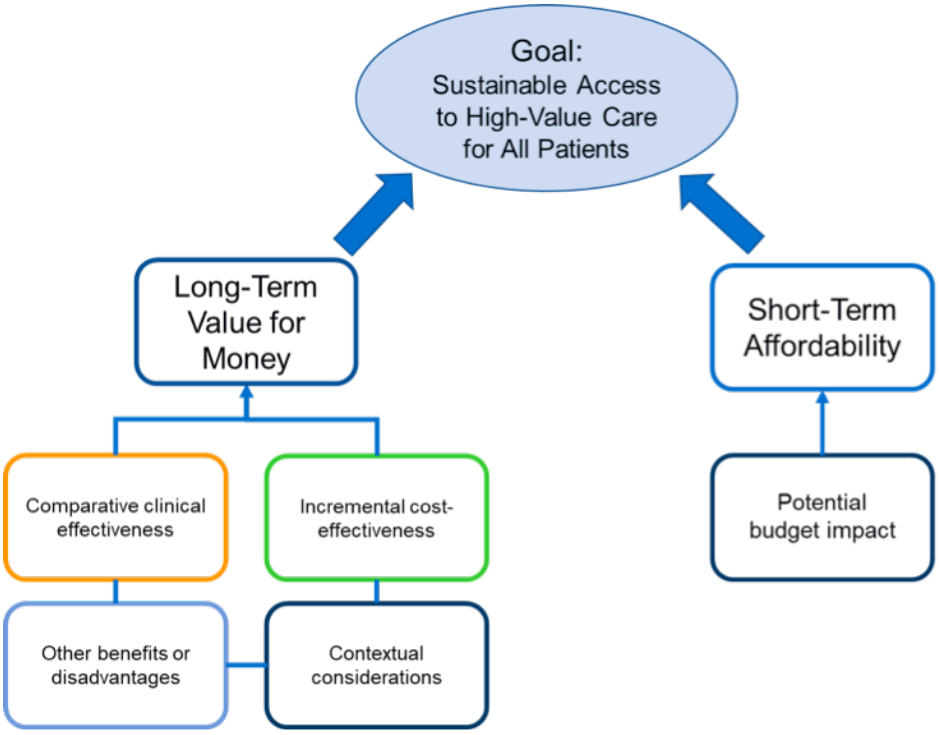
Gene therapies, which can provide cures for diseases, are a new area of research for ICER. Some are within two to three years of becoming available publicly. This is exciting, but also offers serious and critical challenges in valuation. The focus of this seminar is on those challenges.

[1] For more information on ICER, see https://icer-review.org/.

2. Adapting ICER's Approach to Gene Therapy

ICER's standard approach, diagrammed in Figure 1, may need some modification for gene therapies. The goal of our value framework is to assess value in a way that will help ensure sustainable access by all patients to high-value care. We emphasise that the public and private insurance system ("payers" in the US vernacular) must consider both long-term value for money and short-term affordability.

Figure 1. ICER Approach

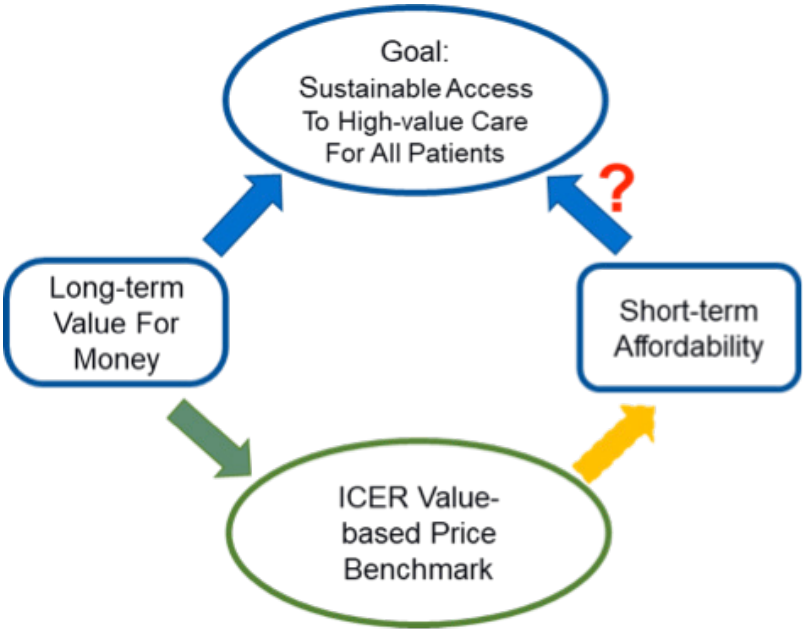


Long-term value has four subdomains. The first two are common in health technology assessment (HTA): (1) comparative clinical effectiveness, i.e. the magnitude of the net health benefit, cost aside, based on available comparative clinical effectiveness information, and (2) incremental cost-effectiveness, with an emphasis on the longer term. The final two components capture factors that might not be part of the cost-effectiveness model or directly obvious from the clinical trial, but still are important: (3) other benefits or disadvantages, considerations that may be difficult or impossible to quantify but are highly important to patients and their families, and perhaps to the health system and society, and (4) contextual considerations, i.e. the social values that affect everything about a review.

Short-term affordability is an analysis of the potential budget impact of the intervention. In ICER's value framework the emphasis is on the longer term, but short-term affordability does, and perhaps should, influence decisions about the introduction of a new intervention. The effect of the concern about short-term affordability is important. If that price is too high, even a product with high long-term value will face a short-term affordability problem, and potentially seriously reduce patient access.

Long-term value for money, then, is the foundation of ICER's value-based price benchmark, using a cost-effectiveness range rather than a single threshold. That circles back to consideration of whether short-term affordability requires special attention from policymakers, as suggested by Figure 2.

Figure 2. ICER Value-based Price Benchmark



3. Four Primary Challenges in Valuing Gene Therapy

Valuing a gene therapy presents four distinct challenges, in addition to pricing per se[2]: (1) inherent limitations on developing data about clinical effectiveness, (2) incorporating important additional elements that are not usually included in cost-effectiveness analysis (CEA), (3) integrating social values into value-based pricing, and (4) producing policy-relevant estimates given the magnitude of gains produced by cures.

3.1. Uncertainty About Clinical Effectiveness

The first challenge is to suggest value-based prices for gene therapies that reflect substantial uncertainty about clinical effectiveness because of one or more factors: limitations in study design, size of the population, and the duration of the studies. This is not a new problem and not unique to gene therapies. The difference is that the value of gene therapy is grounded in whether a one-time, or short-term, treatment will produce a lifelong benefit in practice. If it does that, the benefit would be exceptionally high. The uncertainty about clinical effectiveness will make it considerably more difficult for ICER's reports, released at or near the time of FDA approval, to suggest an appropriate range of prices.

Give the degree of uncertainty, probabilistic sensitivity analyses and other existing approaches will certainly be strained, and perhaps prove insufficient, in suggesting a fair range of prices for a gene

[2] For a discussion on pricing, including innovative approaches, see Hampson et al. (2018) and ICER (2017).

therapy. Linking price to outcomes over the next 20, 30 or 40 years is much more difficult than may appear at first. One challenge is in the technical aspects of modelling the proportion of patients who will be cured successfully and including that in cost-effectiveness assessments and pricing.

In the US, where pilot projects with some gene therapies are about to begin, the plan is to pay in instalment payments over five years. At issue in the US, of course, is that patients may not remain insured by the same payer over time except, perhaps, if they are covered by a federal or state programme. This means that instalments for longer periods are unrealistic. Theoretically, the situation should be easier in single-payer systems, like the NHS, where structuring payments over a longer time period for an individual patient is possible.

3.2. Incorporating Additional Elements of Value

The second challenge is how value-based prices for gene therapies include elements of value that may be important for potential cures, but which are not part of standard cost-effectiveness methods. This is a known problem when assessing cures. Gene therapies, however, will intensify the challenge and require decisions about which ancillary aspects of value should be included in any value-based pricing scheme.

One of the issues here is making trade-offs. If we successfully quantify other aspects of value and include them in QALYs, the cost-effectiveness range may need to be lower in order to fairly represent the opportunity cost of systematically assigning "higher" value to a growing number of interventions. Retaining the same cost-effectiveness threshold would add costs for gene therapies without off-setting that new cost with reduced spending elsewhere. Opportunity costs, then, are real.

ICER's reports have a section entitled "potential other benefits". To decide what to include, we hold discussions with patients' groups, clinical experts and life sciences companies to gather evidence, if possible, or at least insight. For gene therapies, three potential benefits seem particularly relevant: first and only successful treatment, effect on society (schools, the community) and effect on the infrastructure of care. ICER asks its appraisal committees to vote separately on whether each "potential other benefit" is a significant factor for the treatment. The objective is to uncover what the committees believe decision makers ultimately should consider in determining value for money.

ICER has had meetings with stakeholders that specifically identified gene therapies or potential cures as having a significant positive impact socially. This is not only within family but outside of it, including in schools and the community.

An intervention also may have a significant impact on the entire infrastructure of care. An example is Luxturna® (voretigene neparvovec-rzyl), a treatment that is not a cure but is the first highly effective treatment for a genetic form of childhood blindness. Parents recounted that that, until the existence of this treatment, the clinical world ignored them because treatment was not possible. Screening was not done, since no treatment was available, so patients were discovered only by chance.

As a result of this new treatment, parents are no longer alone in their concern; clinicians are learning about it and setting up networks that include early screening and referrals to experts for genetic testing and potential treatment. This changes the infrastructure of care. ICER asks its independent councils vote on the importance of such changes, and we emphasise those votes in our final report.

3.3. Integrating Social Values into Value-based Pricing

Additional elements of value are concerns distinct from social values. Social values are the relative priorities society accords treatment for conditions that are severe, quickly fatal, affect children or entail a high lifetime burden of illness. Incorporating these values into HTA models or QALYs is a familiar challenge; what is new with gene therapies is that such considerations often will not just be a question, but the question. The answers will be anything but easy and the debates will range far beyond the familiar.

ICER asks its independent appraisal committees to take a separate vote on each of the following, which are particularly relevant to gene therapies to signal what may be significant to the ultimate decision maker.

- Is this intervention intended for the care of individuals with a condition of particularly high severity, either in its impact on length of life or quality or life?
- Is it intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness?
- Is it the first to offer any improvement for patients with this condition?

The last question is difficult because it focuses on innovation and raises the issues of whether a special bonus should be awarded for innovation. This is a perennial debate in virtually every country. Gene therapy will certainly raise this issue repeatedly.

One specific example of integrating social values is Luxturna, which some consider the first and only true gene therapy to date. This treatment uses an adeno-virus delivery mechanism injected into the retina; the genetic material enters the genes of the retina and replaces the faulty gene.

This is a fascinating assessment on many levels. First, blindness is difficult to value. Some patients' groups representing the blind emphasised that they consider their quality of life to be as high as a sighted person's; but the sighted community considers becoming blind a serious threat to quality of life. These differences may not be surprising, but they do complicate assessment efforts.

Second, outcomes measures for this inherited retinal disease did not exist when the treatment was being developed. The company that developed it created its own method for diagnostic screening, based on the first symptoms that children with this condition experience, seeing in low light. The child is asked to navigate a floor maze of black and white squares, with unexpected bumps. Scoring is based on how much of the maze the child can complete successfully in a certain amount of time.

Although this is a useful outcome measure, it does not measure quality of life. How long the treatment would remain effective also is unclear. Some of the earliest patients treated have had excellent outcomes at the five-year mark, but that it is not a lifetime. Some experimental evidence from a similar delivery mechanism with a different gene suggested that the effects might dissipate in seven to ten years. If effects do dissipate, it is not clear what the implications might be, i.e. whether vision suddenly returns to baseline or if the slide into blindness is slower.

The uncertainties made HTA particularly difficult, but we did provide estimates: (1) from the health system perspective, $644,000 per QALY and (2) from the societal perspective, where much of the cost impact was from effects on disability, education, productivity at work, etc., $480,000 per QALY. These are exceptionally high cost-effectiveness ratios.

ICER's panel heard testimony and saw these results. The panel voted that the clinical effectiveness evidence was certainly adequate to prove this superior to the usual care. The majority voted that this represented intermediate long-term value for money. This was a fascinating discussion. The panel recognised that, despite high cost-effectiveness ratios, the treatment was the first ever for the condition, changed the infrastructure of care, offered other potential benefits for patients, might allow parents to return to work, and could provide more freedom for a child in daily life.

The list price for Luxturna is $850,000. Treatment requires just one shot, one time. Not surprisingly, every insurer decided to cover it. A major factor in those decisions was that, before FDA approval, the company worked with payers on payment issues. One of these was developing a way to pay a flat fee to physicians for administering the drug, which in the US can double the cost of treatment. Another was payment based on a relatively short outcome so that if the child's vision has not improved within 90 days, then the payer receives a rebate, which basically is a discount.

It is viewed as a success in the US market that a drug at this price was accepted by payers – not with glee in terms of the price, because many of them did believe it was too expensive, but at all. Payers appreciated that the company had shown good faith working with them to address how the payment mechanism might take account of uncertainties about duration of efficacy and concerns about budgetary impact.

Two CAR-T drugs, Kymriah® and Yescarta® provide a second case study (although not everyone agrees that these are truly genetic therapies). List prices in the US are $475,000 for paediatric leukaemia and $373,000 for adult non-Hodgkin's lymphoma. The drugs now both are approved for treatment of non-Hodgkin's lymphoma, but were not when ICER first assessed them.

CAR-T therapy costs are higher than the price for the drug alone suggests. Ancillary drugs and other treatments are required for many patients to address severe side-effects; in some cases, expensive treatments are necessary, for example, to keep white cells at the desired level. The actual cost of treatment, then, is closer to $600,000–$700,000.

ICER's assessment was that Kymriah, for paediatric leukaemia had a QALY of $46,000; Yescarta, indicated for non-Hodgkin's lymphoma, had an ICER cost-effectiveness ratio of $136,000 per QALY. Some stakeholders were both shocked and disappointed, not because of the numbers per se, but because of the numbers in the current political context in the US. Drug prices continue to be highly controversial and some complained that ICER concluded that a drug this expensive could be considered reasonably priced. This in turn has triggered public angst over whether cost-effectiveness is the proper tool to use to suggest prices for the drugs. Should price not be based instead on what it costs to make the drug, with a small profit on top of that?

Public discussion about pricing and value was a useful process for ICER. It allowed us to emphasise that the tools we use to suggest value are not meant to find that prices are too high, but are meant instead to help distinguish which treatments provide good clinical value for the money. The fact that a drug this expensive can be found to be highly cost-effective is, in a sense, a critically important message for our health care system to hear.

The ICER independent panel heard the discussions about potential other benefits from patients and clinical experts, as is our usual process. It voted that Kymriah, at $46,000 per QALY, provided intermediate long-term value for money, but not high long-term value despite being a first effective

treatment. The reason was the uncertainty about the how long the treatment would remain effective in a patient.

For Yescarta, ICER suggested a range of $100,000 to $150,000 per QALY. At $136,000, the panel rated it as between intermediate and low value, again because of uncertainty about the duration of effect. This shows how ICER's value framework operates — the cost-effectiveness ratio is not intended to be the sole determining factor.

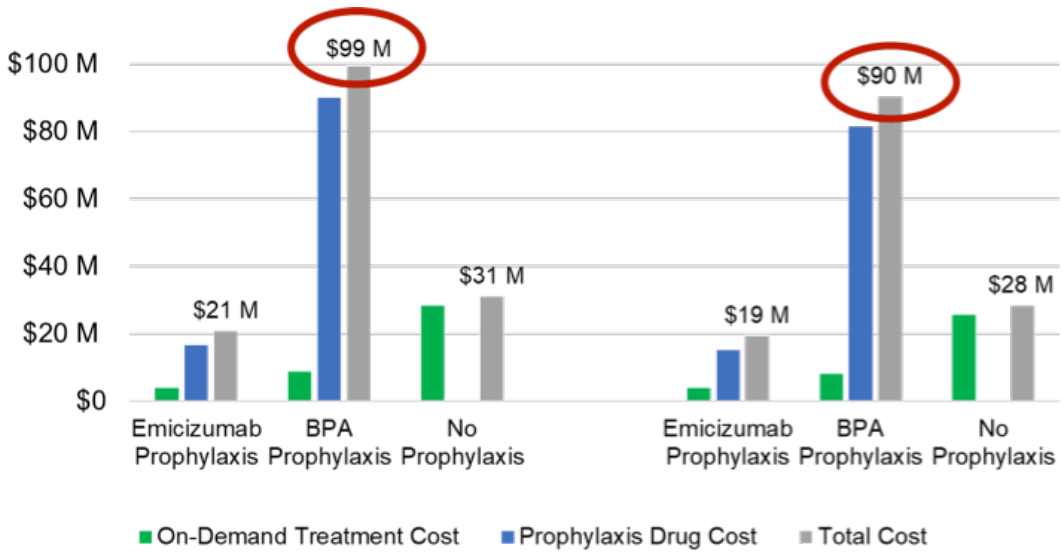
The coverage and payment experience for these drugs has been problematic. The idiosyncratic features of the payment structure in the US make it difficult for insurers to determine how to pay hospitals enough to cover the ancillary services needed for this treatment. Hospitals initially were taking a substantial financial loss with each treatment; over 200 patients now have been treated and this problem still is not fully resolved

3.4. Producing Policy-relevant Estimates for Cures

The first three challenges are ones that are well known, but the fourth is one that is not: how prices can capture the magnitude of heath gain offered by cures, gains that far exceed those of other interventions. Pricing a treatment that rates high in QALYs can produce results that may just not be policy relevant.

To illustrate this challenge, Figure 3 is based on an ICER view of emicizumab. This not actually a cure, but it is being used in a therapeutic area where cures are in development and progressing well. Emicizumab is a treatment for children with haemophilia A who require bypassing agent prophylaxis. Treatments are intended to prevent bleeding; patients who bleed then take more of the drug.

Figure 3. Lifetime Costs of Haemophilia A Requiring Bypassing Agent (BPA) Prophylaxis



The vertical axis in Figure 3 is tens or twenties of millions of dollars in lifetime costs; the horizontal axis shows options for prophylaxis; and the grey bars in the middle represent current best care before the availability of emicizumab. The graph on the left is costs for children; the one on the right is for adolescents. In the US context, then, the average child with haemophilia A who needs

bypassing agents would require $99 million in health care spending in their lifetime. Nearly all of that is for the treatments themselves — extraordinarily expensive treatments. Let us assume a cure for such patients is developed, a one-time treatment. Cost-effectiveness, based on savings over a lifetime, and using non-discounted figures, would suggest a $99 million price tag.

This is one dramatic example of the issues that cures, or potential cures, will raise for standard cost-effectiveness tools. Clearly, in such instances, full price based on the standard cost-effectiveness willingness-to-pay threshold will not be policy relevant. The argument likely will be that pricing should be based on "fair profit," i.e. the cost of production with an innovation bonus, perhaps even explicitly factoring in failures and the costs of clinical trials.

Other options might be discussed. For example, if the cost offset is the major factor in suggesting an exceptionally high price, a price cap might be set on the price paid for health gain (a "QALY cap"). Then the cost offset becomes irrelevant. Or, finally, a "shared savings" approach might be adopted. This is common in the US now, particularly between physicians and hospitals where contracts agree that each party shares savings produced through cooperative programs that are intended to reduce costs but maintain quality.

As an example of what these alternative options would entail, assume a new cure for a fatal disease for a five-year-old child who would die in ten years using existing standard resistant therapy. Assume the willingness-to-pay threshold is $100,000 per QALY and that the standard therapy costs $100,000 per year but even with the therapy the child still will die in 10 years.

Figure 4 summarises the pricing options. The first row is standard CEA. The cost of current therapy is $100,000. If this cure were to allow children to live to age 65 on average, the QALY gain (undiscounted) would be 50 QALYs. The QALY gain price for that, at the rate of $100,000 for 50 QALYs, is $5 million. The cost offset of not spending $100,000 for each of the 10 years that the child otherwise would have lived is an additional $1 million. Thus the value-based price using the standard CEA approach would be $6 million

Figure 4. Options for Value-Based Pricing of a Cure – 1

- New cure for fatal childhood disease of a 5-year-old child who would die in 10 years with standard therapy
- Assumed willingness-to-pay threshold of $100,000 per QALY

	Cost per year of current drug	QALY gained	QALY gain price	Cost offset price component	"Value-based" price
Standard CEA	$100,000	50	$5 million	$1 million	$6 million
QALY price cap	$100,000	50	$5 million	$0	$5 million
Shared savings 50%	$100,000	50	$5 million	$500,000	$5.5 million
Shared savings 75%	$100,000	50	$5 million	$250,000	$5.25 million

Imposing a QALY price cap produces a $5 million price. Shared savings, depending on how costs are shared, produces pricing suggestions between $5.25 million and $5.5 million in this example.

The purpose of this illustration is not to suggest an answer, but to point out how policy makers may be thinking about pricing for cures. All these prices are high. Perhaps factoring in uncertainty offers another opportunity – a specified amount of uncertainty might halve the attributed QALY gain, for example. But we are at the early stage of even discussing whether some version of these alternatives would be accepted. The point is that much remains to be done to sort out how to address these issues.

Figure 5 illustrates a different type of condition, a non-fatal, chronic disease with a baseline utility of 0.2 each year for 50 years. As in the previous example, the willingness-to-pay threshold is $100,000 and standard therapy for this chronic condition costs $100,000 per year. In this case, however, the spread of pricing using alternative approaches is larger. (It is coincidence that the first row produces the same value-based price.) The health gain with treatment is 10 QALYs, which alone would suggest a value-based price of $1 million; because this patient would have lived for a full 50 years at $100,000, the cost offset is $5 million. That produces a traditional value-based price of $6 million. Capping the price of the QALY gain would keep the price at $1 million, obviously a big difference. Sharing the cost offsets 50:50 would mean a price of $3.5 million; at 75:25, it would be $2.25 million

Figure 5. Options for Value-Based Pricing of a Cure – 2

- New cure for a non-fatal chronic with utility gain of 0.2 per year for 50 years
- Assumed willingness-to-pay threshold of $100,000/QALY

	Cost per year of current drug	QALY gained	QALY gain price	Cost offset price component	"Value-based" price
Standard CEA	$100,000	10	$1 million	$5 million	$6 million
QALY price cap	$100,000	10	$1 million	$0	$1 million
Shared savings 50%	$100,000	10	$1 million	$2.5 million	$3.5 million
Shared savings 75%	$100,000	10	$1 million	$1.25 million	$2.25 million

Discussions with a variety of audiences are important to discerning which, if any, of the possible approaches identified to date are fit for purpose. The criteria or principles on which to base decisions to use a non-traditional approach to valuation still need to be decided. For example, in a shared savings approach, what might guide the decision about how to split cost-offsets between the innovator and the health system or society?

A list of possible criteria or principles might include any or all of the following:

- *Relative uncertainty about how long the therapeutic benefit will continue (durability)*
  A system for rating uncertainty might even be quantitative, an approach that has not yet been developed.
- *Magnitude of the health gain and/or cost offset*
  A scale might be needed also for indicating the magnitude of health gain or cost offset that could be shared, one that may go beyond cost-effectiveness to consider softer issues of "fairness".

- *Extent of federal investment in the basic science*
  Calls for paying a return to government on its initial investment in the science have become louder recently.
- *Size of the intended population*
  Population size obviously is one determinant of budgetary impact; sharing might need to be inversely related to the size of the population.
- *Option to pay through instalments*
  Cost-effectiveness provides guidance on pricing, but no suggestions about payment. Perhaps what is needed is a system to modulate payment, or perhaps pricing and payment solutions need to be developed coincidentally. The two examples above showed the standard CEA at $6 million. Panic and protest might be the initial reaction to such a price; would $600,000 each year for ten years be acceptable to a payer or health economists, for example?

Although these issues are clearly crucial for the therapies discussed in this seminar – gene-based cures – working through them inevitably will affect thinking about current approaches to assessing treatments that might not offer a cure but still produce substantial health gains and cost offsets. This may be good news and bad news; new approaches may produce better assessments, but they may also raise questions about whether existing assessment, at least for some treatments, should be revisited.

4. The Future is Now

A new agent, AVXS-101, offers a final illustration of the complexity of the issues. This is ICER's fourth involvement in assessing a gene therapy drug. AVXS-101 is a treatment for spinal muscular atrophy, a rare condition commonly known as "floppy baby syndrome". Cases vary in severity, but many children die in adolescence because their muscles continue to weaken and they cannot breathe.

The standard of care has recently been revolutionised by the advent of nusinersen, a relatively effective new treatment, and the first of its kind for this condition. It is priced at $750,000 for the first year and about $350,000 each year after that for the rest of the patient's life. Obviously, that is a huge investment over a lifetime. AVXS-101 may reduce or eliminate the need for nusinersen and provide similar or better clinical effectiveness.

ICER is in the midst of its evaluation so details about our results to date are confidential. The challenges, however, are familiar. As usual, we are considering how to best measure efficacy and are gathering input on potential other benefits and contextual considerations. The key questions for this assessment are, first, the duration of clinical effectiveness, which is a critical question given the lifetime use required for nusinersen and, second, pricing. Nusinersen has become the standard of care since it became available a year ago because it is the only treatment. Should the value-based price of AVXS-101 be predicated on its clinical effectiveness versus nusinersen or versus supportive care, which was the standard of care just 18 months ago? What if AVXS-101 itself is not cost-effective? Issues also arise about the cost offset for AVXS-101. Should it be the full total of initial and continuing treatment with nusinersen? If the costs of nusinersen are considered as standard of care and are fully offset by AVXS-101, traditional cost-effectiveness might suggest that AVXS-101 is the first drug to merit a value-based price over $10 million. Would that be the "right" recommendation?

The hypothetical questions noted earlier are hurtling forward in this review at a dizzying speed, requiring us to address a wide range of technical, methodological, procedural and ethical issues. The need to decide rather quickly on workable approaches is urgent and not only for AVXS-101. In the next three years alone, potential gene-based cures are expected to be available for haemophilia A, sickle-cell anaemia, β-Thalassemia and muscular dystrophy. That cures may be available is wonderful news; what is concerning is that we are not yet prepared to provide the input essential for policy making.

ICER is well aware that finding answers will require cooperative efforts; we expect to be working with NICE, for example, and look forward to engaging in discussion with as many others as possible, including the life sciences companies and health economists participating in this seminar. The challenge is no longer approaching through a mist in the distance; it is on top of us and will all too soon be visible in the rear-view mirror.

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