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Methodology

Does Cost-Effectiveness Analysis Overvalue Potential Cures? Exploring Alternative Methods for Applying a "Shared Savings" Approach to Cost Offsets

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Editor's Note: This article has an accompanying editorial, *Valuing Cures: Not If, But When?*, which is published elsewhere in this issue.

ABSTRACT

Objectives: To evaluate alternative methods to calculate and/or attribute economic surplus in the cost-effectiveness analysis of single or short-term therapies.

Methods: We performed a systematic literature review of articles describing alternative methods for cost-effectiveness analysis of potentially curative therapies whose assessment using traditional methods may suggest unaffordable valuations owing to the magnitude of estimated long-term quality-adjusted life-year (QALY) gains or cost offsets. Through internal deliberation and discussion with staff at the Health Technology Assessment bodies in England and Canada, we developed the following 3 alternative methods for further evaluation: (1) capping annual costs in the comparator arm at $150 000 per year; (2) "sharing" the economic surplus with the health sector by apportioning only 50% of cost offsets or 50% of cost offsets and QALY gains to the value of the therapy; and (3) crediting the therapy with only 12 years of the average annual cost offsets or cost offsets and QALY gains over the lifetime horizon. The impact of each alternative method was evaluated by applying it in an economic model of 3 hypothetical condition-treatment scenarios meant to reflect a diversity of chronicity and background healthcare costs.

Results: The alternative with greatest impact on threshold price for the fatal pediatric condition spinal muscular atrophy type 1 was the 12-year cutoff scenario. For a hypothetical one-time treatment for hemophilia A, capping cost offsets at $150 000 per year had the greatest impact. For chimeric antigen receptor T-cell treatment of non-Hodgkin's lymphoma, capping cost offsets or using 12-year threshold had little impact, whereas 50% sharing of surplus including QALY gains and cost offsets greatly reduced threshold pricing.

Conclusions: Health Technology Assessment bodies and policy makers will wrestle with how to evaluate single or short-term potentially curative therapies and establish pricing and payment mechanisms to ensure sustainability. Scenario analyses using alternative methods for calculating and apportioning economic surplus can provide starkly different assessment results. These methods may stimulate important societal dialogue on fair pricing for these novel treatments.

Keywords: cost-effectiveness, cures, economic surplus, cost offsets.

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Introduction

There are a growing number of emerging treatments that are eagerly anticipated because of their potential to cure or substantially mitigate a wide range of conditions.[1] Nevertheless, especially for single or short-term therapies (SSTs), traditional cost-effectiveness methods that apportion to the therapy all incremental quality-adjusted life-year (QALY) gains and all projected lifetime cost offsets have been noted as potentially supporting value-based pricing of $25 million or higher).[2-5]

Innovative payment arrangements based on some form of installment payment could potentially improve the affordability of prices of this magnitude, but it is also reasonable to question whether traditional cost-effectiveness methods are fit for the purpose of evaluation of SSTs. The traditional approach assigns full credit to the new therapy for (discounted) lifetime health gains and cost offsets. In part, this approach has been justified by the implicit balance that occurs between the economic surplus retained by the innovator in the early years after launch and the economic surplus enjoyed by patients and the health system in

the decades that follow the end of marketing exclusivity, a period during which price reductions from generic competition are expected. Nevertheless, many SSTs are likely to be cell and gene therapies for which there may never be generic competition, shifting the balance of the long-term economic surplus to the innovator. Combined, the potential for extremely high valuations of some SSTs and the risk that generic competition will not emerge have led some to suggest the need for alternatives for the allocation of economic surplus generated by these types of innovative therapies.[3]

Our objective in this article is to analyze the rationale behind several different alternative methods to calculate or distribute economic surplus for SSTs. We also describe potential advantages and disadvantages of these approaches and evaluate their impact in scenarios of several potentially curative therapies.

Methods

Literature Search

We first performed a systematic literature review seeking articles on alternative methods for cost-effectiveness analysis (CEA) of cell and gene therapies or other treatments that could be considered potential cures. We searched Medline, Embase, Health Technology Assessment (HTA) database, National Health Service Economic Evaluation Database, and the CEA Registry for English-language publications from December 2004 to February 2019 with keywords related to cures, cell and gene therapy, and/or regenerative medicine. We also reviewed relevant literature from conference proceedings. Furthermore, we had in-depth discussions with staff from the National Institute for Health and Care Excellence (NICE) in the United Kingdom and from the Canadian Agency on Drugs and Technology in Health (CADTH). The NICE had previously explored methods and issues related to evaluation of chimeric antigen receptor T-cell (CAR-T) therapy, and the CADTH provided input based on their consideration of approaches to the economic evaluations of cell and gene therapies.[4,5]

Evaluation of Alternative Methods

The systematic literature review revealed little published material specifically addressing potential alternative methods for the CEA of potential cures.[6] Alternative methods described were almost universally related to evaluating uncertainty and to the discount rates applied on health and economic outcomes. We did not select for further evaluation of the conceptual approach to "rate of return" pricing for potentially curative SSTs as suggested by Drummond and Towse.[7] We felt that this approach was infeasible as a method for HTA bodies because it would require contribution of development cost information for each SST, information that is neither known by life science companies nor likely to be divulged even in broad estimates.

Although affordability of SSTs was highlighted as a concern by many sources, measures to address this concern, such as innovative payment mechanisms, were assumed to be applied post hoc after (or without reference to) traditional CEA. We therefore developed 3 new alternative methods that could, in different ways, address the core issue of the magnitude of the economic surplus and/or its apportionment between the therapy and the health sector. These 3 alternative methods are described in detail in subsequent discussion. To evaluate the impact of these alternative methods on different scenarios related to the chronicity of condition and the magnitude of potential cost offsets, we applied the alternative methods to 3 cost-effectiveness models that had been previously developed in collaboration with external, independent academic modelers for previous incremental cost-effectiveness ratio asssessments by our HTA organization, the Institute for Clinical and Economic Review (ICER).[8-10] For each model, we retained the same time horizons (lifetime), perspective (healthcare sector), and efficacy and cost inputs as in the original analyses. Each model is described briefly subsequently, with more details available in the published reports in which they were originally featured.[8-10]

Scenario 1: a short-term fatal pediatric condition

The original model for this scenario was developed by academic collaborators at the School of Health and Related Research, University of Sheffield, in the United Kingdom for the purpose of evaluating onasemnogene abeparvovec (Zolgensma®, Avexis, Bannockburn, IL) compared with best supportive care for treatment of spinal muscular atrophy (SMA) type 1.[8] The model was developed before the launch of Zolgensma and assumed a one-time price of $2 million. The model contained the following 2 main components: a short-term model concordant with clinical study data and a long-term model that extrapolated longer-term motor function milestones, permanent ventilation status, and mortality rate. The model assumed that motor function milestones achieved at the end of follow-up in the clinical trials were sustained until death.

Scenario 2: a chronic condition with substantial cost offsets

The model used for this scenario was created by academic collaborators at the School of Pharmacy, University of Washington, in Seattle to compare the cost-effectiveness of emicizumab (Hemlibra®, Genentech, South San Francisco, CA) prophylaxis with 2 alternative strategies for patients with hemophilia A with inhibitors to factor VIII who will not be treated with immune tolerance induction or for whom immune tolerance induction has been unsuccessful.[9] For this exercise, we modeled a hypothetical one-time treatment with emicizumab for patients aged 12 years and above. To ensure comparability with our original analysis, the base case for the adapted model did not assume that the hypothetical treatment would cure patients but that a single administration would have the same effectiveness in reducing bleeds as emicizumab did. We arbitrarily chose a $5 million price for this hypothetical one-time treatment. Note that this price is provided as a demonstration only and may be viewed by some as an extreme scenario; however, a gene therapy currently under development for hemophilia A has been forecast to have a launch price up to $3 million.[11]

Scenario 3: a short-term fatal condition among adults

The model for this scenario was developed by academic collaborators at the Skaggs School of Pharmacy, University of Colorado, in Denver to evaluate the cost-effectiveness of axicabtagene ciloleucel (Yescarta®, Kite, Santa Monica, CA), a CAR-T therapy, versus chemotherapy in adults with refractory aggressive B-cell lymphoma who are ineligible for autologous stem cell transplant.[10] Patient survival was calculated from available Kaplan-Meier curves from key trials that were digitized and extrapolated upto 5 years after treatment initiation, at which point those alive and responding to treatment were considered effectively cured (ie, exhibited mortality consistent with the general population). Those alive and not considered cured at 5 years transitioned to palliative chemotherapy.

Table 1. Different approaches to value-based prices for Zolgensma in SMA type 1.

Zolgensma (assuming one-time $2 000 000 placeholder price) vs BSC	Costs	QALYs	Cost per QALY gained	Value-based price at $150 000/QALY
Base case (no shared savings)				
Zolgensma	$3 657 000	12.23	$243 000	$899 000
BSC	$789 000	0.46		
Incremental	$2 868 000	11.77		
Cost offset $150 000/y cap				
Zolgensma	$3 657 000	12.23	$250 000	$825 000
50% cost offset				
Zolgensma	$3 657 000	12.23	$277 000	$504 000
BSC	$395 000	0.46		
Incremental	$3 262 000	11.77		
50% cost + QALY offset				
Zolgensma	$3 657 000	6.12	$554 000	—*
BSC	$395 000	0.23		
Incremental		5.89		
LOE cost offset scenario				
Zolgensma	$3 657 000	12.23	$303 000	$195 000
BSC	$85 000	0.46		
Incremental	$3 572 000	11.77		
LOE cost + QALY scenario				
Zolgensma	$3 657 000	1.32	$2 805 000	—*
BSC	$85 000	0.05		
Incremental	$3 572 000	1.27		

BSC indicates best supportive care; LOE, loss of exclusivity; QALY, quality-adjusted life-year; SMA, spinal muscular atrophy.
*No positive price could be calculated that would achieve $150 000 per QALY threshold.

Alternative Methods for Calculating or Apportioning Economic Surplus

Capping annual cost offsets

For chronic illnesses, a one-time curative treatment may obviate the need for expensive care in many years. In such situations, traditional assessment methods could find an extremely high price for a new treatment that meets established cost-effectiveness thresholds. Conceptually, this is of even greater concern when the baseline care costs in the comparator arm—the costs that will be prevented and thus folded into the economic surplus granted the new therapy—are themselves too high to be cost-effective. One way to address this issue would be to "re-price" the comparator arm in the modeling so that it meets an acceptable cost-effectiveness threshold. Nevertheless, doing so is unlikely to be possible based on available evidence, so the approach we evaluated is to cap annual cost offsets attributed to an SST to the operative threshold price for an additional QALY. On the basis of existing value framework of ICER, we set the cost offset cap at $150 000 per year, the upper boundary of our cost per QALY pricing benchmark.

Sharing economic surplus

Another method to address concerns that the magnitude of the economic surplus attributed to an SST is too high when following traditional cost-effectiveness methods is to apportion the surplus differently between the therapy/innovator and the health sector. We suggest that in the context of the United States the "health sector" should be considered to be those responsible for paying for health insurance; thus patients, payers, and health plan sponsors (including tax payers for public insurance programs) would retain a proportional share of economic surplus by reduction in the launch price of the new treatment. In a recent article on valuing cures, we named this a "shared surplus" approach in which innovators would get some, but not all, of the economic surplus traditionally folded into the "cost-effective" price of new treatments.[12]

Capping economic surplus at the time threshold for loss of exclusivity

Another approach that would effectively let the health sector retain more of the economic surplus through lower launch prices is to cap the number of years during which the therapy/innovator is assigned 100% of the surplus. As a conceptual target for this time threshold, we chose the time at which a new SST might be presumed to reach its patent and/or exclusivity cliff after launch.[13] Selecting this time threshold attempts to account for a distinguishing feature of SSTs such as cell and gene therapies: they are less likely to face generic or biosimilar competition compared to traditional drugs, and therefore SSTs will capture more of the long-term economic surplus than if they faced generic/biosimilar competition in later years.[13] We selected a 12-year period as an estimate of the average length of time expected for loss-of-exclusivity (LOE) periods.[14-18] This time threshold corresponds with the 12-year period of exclusivity granted to new innovative biologics in recent US legislation, a time period which has been found to provide a handsome investment return to innovators in analyses of a representative biologic in its life cycle.[19]

Although the LOE phase occurs during the years immediately after regulatory approval, for some treatments, such as a one-time treatment that prevents the late onset of Alzheimer's disease, it is possible that all or most of the cost offsets or QALY gains in a CEA

Table 2. Value-based price on the basis of cost-offsets captured for hypothetical SST in hemophilia A.

Hypothetical SST (assuming one-time $5 000 000 price) vs BPA prophylaxis	Costs	QALYs	Cost per QALY gained	Value-based price at $150 000/QALY
Base case (no shared savings)				
Hypothetical Tx	$9 269 000	15.41	Cost-saving	$86 000 000
BPA prophylaxis	$90 182 000	15.21		
Incremental	–$80 913 000	0.20		
Cost offset $150 000/y cap				
Hypothetical Tx	$9 269 000	15.41	$7 262 000	$3 612 000
BPA prophylaxis	$7 852 000	15.21		
Incremental	$1 418 000	0.20		
50% cost offset				
Hypothetical Tx	$9 269 000	15.41	Cost-saving	$40 851 000
BPA prophylaxis	$45 091 000	15.21		
Incremental	–$35 822 000	0.20		
50% cost + QALY offset				
Hypothetical Tx	$9 269 000	7.71	Cost-saving	$40 836 000
BPA prophylaxis	$45 091 000	7.61		
Incremental	–$35 822 000	0.10		
LOE cost offset scenario				
Hypothetical Tx	$9 269 000	15.41	Cost-saving	$12 916 000
BPA prophylaxis	$17 157 000	15.21		
Incremental	–$7 888 000	0.20		
LOE cost + QALY scenario				
Hypothetical Tx	$9 269 000	5.14	Cost-saving	$12 891 000
BPA prophylaxis	$17 157 000	5.08		
Incremental	–$7 888 000	0.06		

BPA indicates bypassing agents; LOE, loss of exclusivity; QALY, quality-adjusted life-year; SST, short-term therapy; Tx, treatment.

would occur after the initial 12-year period. To account for this, in our modeling scenarios testing this approach we used the average annual cost offset and/or QALY gain over a lifetime horizon, allocating 12 years of the average surplus to the therapy/innovator and the remainder to the health sector.

Results of Analyses Using Alternative Methods

In the subsequent discussion, we present the results revealing the impact of the different alternative methods on ICERs and threshold pricing at $150 000 per QALY for each of the 3 selected condition-treatment scenarios, with costs and cost-effectiveness ratios rounded to the nearest $1000.

Scenario 1: A Short-Term Fatal Pediatric Condition

For Zolgensma in SMA type 1, capping cost offsets at $150 000 per year had minimal impact on total costs, producing a small decrease in the threshold price, from $899 000 in the base case to $825 000 using the alternative method (Table 1). The threshold price decreased far more substantially, to $504 000, with 50% sharing of cost offsets between the therapy and the health sector. When the QALYs gained were also included at a 50% sharing ratio, the ICER increased to more than $500 000 per QALY and no price could be calculated to reach the $150 000 per QALY threshold owing to the smaller incremental QALY gains from treatment.

The LOE time threshold method created the largest difference in the threshold price, dropping it down to $195 000 when cost offsets were capped at 12 years, and resulting in no possible price at which the therapy would reach a threshold of $150 000 per QALY when QALY gains and cost offsets were both capped at 12 years. The dramatic effect of the LOE time threshold approach in this scenario is largely owing to the high mortality rate of patients in the comparator arm of the model.

Scenario 2: A Chronic Condition With Substantial Cost Offsets

Supportive care for hemophilia A for patients with inhibitors is extremely expensive, and thus traditional cost-effectiveness methods suggest that a threshold price for a one-time treatment that can prevent the need for much of this care is extraordinarily high: $86 million in the base case (Table 2). Capping cost offsets at $150 000 per year had the greatest impact on the threshold price in this scenario, reducing it to $3.6 million, as the annual cost of bypassing agent prophylaxis in the comparator arm is well above $150 000 per year.

Applying the 50% shared surplus alternative method produces a lower threshold price of $41 million. When QALY gains were added to the 50% sharing method, the threshold price decreased further only slightly. The LOE time threshold method produced a threshold price of $12.9 million, reflecting the large impact of reducing cost offsets for more than 12 years owing to the relatively long lifespan of these patients. The LOE scenario adding QALY gains to cost offsets did not change the results significantly.

Scenario 3: A Short-Term Fatal Condition Among Adults

For Yescarta versus chemotherapy (Table 3), in the treatment of adult B-cell lymphoma, capping cost offsets at $150 000 per year had no impact on the threshold price, as annual costs in the comparator arm never exceeded $150 000. Applying the 50%

Table 3. Value-based price on the basis of cost-offsets captured for Yescarta in adult B-cell lymphoma.

Yescarta (assuming one-time $473 000 cost) vs chemotherapy	Costs	QALYs	Cost per QALY gained	Value-based price at $150 000/QALY*
Base case (no shared savings)				
Yescarta	$617 000	5.87	$136 000	$424 000
Chemotherapy	$155 000	2.48		
Incremental	$462 000	3.4		
Cost offset $150 000/y cap				
Yescarta	$617 000	5.87	$136 000	$424 000
Chemotherapy	$155 000	2.48		
Incremental	$462 000	3.4		
50% cost offset				
Yescarta	$617 000	5.87	$159 000	$340 000
Chemotherapy	$77 000	2.48		
Incremental	$539 000	3.4		
50% cost + QALY offset				
Yescarta	$617 000	2.94	$318 000	$66 000
Chemotherapy	$77 000	1.24		
Incremental	$539 000	1.7		
LOE cost offset scenario				
Yescarta	$617 000	5.87	$143 000	$399 000
Chemotherapy	$131 000	2.48		
Incremental	$486 000	3.4		
LOE cost + QALY scenario				
Yescarta	—	—	—[†]	—[†]
Chemotherapy	—	—		
Incremental	—	—		

LOE indicates loss of exclusivity; QALY, quality-adjusted life-year.
*Does not include hospital markup.
[†]Could not be calculated for this model.

shared surplus approach, the threshold price decreased modestly from $424 000 in the base case to $340 000. Nevertheless, when QALY gains were also included in the economic surplus to be shared, the threshold price decreased markedly to $66 000.

Using the LOE time threshold approach, the threshold price decreased minimally to $399 000. This was not unexpected given that most patients with this condition will likely not survive more than 12 years in the comparator arm. Owing to the underlying structure of this model, we were unable to calculate the threshold price under these methods when both cost offsets and QALY gains were included.

Discussion

The aim of this research effort was to explore the impact of alternative modeling approaches for evaluating new SSTs that, if potentially curative, may be modeled as producing extremely high QALY gains and cost offsets. Any treatment that can produce substantial QALY gains and/or cost offsets is highly desirable, but when using CEA to suggest reasonable pricing, the results can seem so far out of scale with current pricing in the healthcare system that policy makers may question the underlying fairness of how economic surplus is currently apportioned in traditional cost-effectiveness approaches and may ultimately reject the use of CEA entirely.

Market dynamics for cell and gene therapies, which are the archetype for the new wave of potentially curative SSTs, also suggest the need for reconsidering how the economic surplus generated by these treatments is shared between the innovator and the health system. The science underlying cell and gene therapies may make them less likely to face "generic" competition over time, and, therefore, the traditional balance assumed for most new treatments may be thrown off between the initial time period when the innovator retains most of the economic surplus and the latter period when most of the surplus is retained by the health system.[13-18]

Although cost-effectiveness analyses and value-based pricing may not determine coverage and reimbursement decisions for most health technologies, payers in many different countries and within different health systems look to HTA assessments to inform their decisions and they are eager for guidance on new SSTs. Payers have expressed concerns on several factors likely to be relevant for SSTs, such as uncertainty in durability of effect, difficulty in generating robust clinical evidence, and short-term affordability concerns.[20] Such uncertainties have led to increased interest in alternative payment arrangements for such treatments among the payer community and policy makers. Whether actively used in decision making by payers in the United States, economic value evaluation using alternative methods may be relevant for future use or for larger policy discussions on pricing and payment arrangements for SSTs within and outside the United States.

For these reasons, we believe that it is important to explore alternative methods for calculating and apportioning the economic surplus for SSTs. To explore alternative methods, we adapted 3 previously developed cost-effectiveness models and applied several different approaches. Our goal was not only to analyze the conceptual validity of alternative methods but also to evaluate their potential impact on cost-effectiveness results across different types of treatment-condition scenarios.

The alternative methods we evaluated were based on different views of what the "problem" is with the high valuation of SSTs related to extreme economic surplus. First, if the economic surplus is perceived to be unreasonably high primarily because of existing extremely expensive care whose cost will be folded into threshold pricing, then there is a strong rationale to explore an alternative method of capping cost offsets at some figure (we used $150 000 per year). Nevertheless, if the main problem with the economic surplus is that too much of it is apportioned to the innovator, then an argument could be made for either a proportional sharing method (we used a 50% split) or a method that sets a specific time frame after which the surplus is largely retained by the health sector (we used the average LOE period for most drugs of 12 years). It should also be noted that other approaches to how or with whom the surplus should be shared are possible. For example, in cases in which treatments are developed based largely on basic research funded by the National Institutes of Health, it could be argued that surplus sharing should include this agency or the federal government.

The specific figures we used in testing each of these alternative methodological approaches are, to some extent, arbitrary. Capping cost offsets could be set at a higher or lower threshold; a 50% sharing level could be set at 25% or 75% or at any other figure, perhaps based on other factors, such as scale of federal investment in the research and development of the product. The 12-year LOE threshold has the strongest rationale for a specific figure, but the time threshold could also be varied. The goal of the analysis was not to suggest normative figures within each alternative method but to provide a starting point through which to explore each method and its impact when tested in models of different types of conditions with varying expected length of life and baseline care costs.

The results of our analyses revealed that the impact of each alternative method varied widely across therapeutic area and target populations. The alternative method that had the biggest impact on the threshold price for Zolgensma for the fatal pediatric condition SMA type 1 was the 12-year LOE method. For the model of a hypothetical one-time treatment for hemophilia A, an archetype of a chronic, expensive condition, it was capping cost offsets at $150 000 per year that had the biggest impact on the threshold price. For the model of CAR-T treatment of B-cell lymphoma, a fatal adult condition, a 50% sharing of the economic surplus including QALY gains and cost offsets sent the threshold price down from $424 000 to $66 000.

Thus, the impact of different alternative methods for calculating or apportioning economic surplus will depend greatly on the type of condition and its costs of usual care. Because there is no consensus on whether alternative methods are needed in the first place, it may be reasonable to present multiple alternative results for policy makers as additional scenario analyses when considering potentially curative SSTs.

Conclusion

It could be argued that standard methods of CEA are fully capable of evaluating SSTs, as the challenges may be similar in nature, if not in degree, to those of evaluating treatments for rare conditions.[21] Methodologists and HTA bodies have adopted various approaches to address these challenges in the past, and some may feel that these methods are adequate to manage the issues that may seem unique when evaluating potentially curative SSTs.

The goal of this analysis was not to promote a canonical new approach to replace current standard assessment methods but to provide an analytic foundation to support further discussion among health economists, HTA bodies, policy makers, and other stakeholders of approaches to retain cost-effectiveness as a key guide to appropriate pricing for SSTs. All involved desire an approach to pricing and payment that will support robust development of innovative treatments without financially crippling the healthcare system. There is no straightforward solution, and further work is needed to explore how CEA can best inform discussions on the pricing of these innovative treatments in a manner that will ultimately prove affordable and sustainable.

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