Value Assessment Methods and Pricing Recommendations for Potential Cures: A Technical Brief

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ICER Modeling Collaborators

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1. Introduction

1.1 Do We Need New Approaches to Evaluate Potential Cures and Other Transformative Therapies?

Cures are coming. Whether labeled as gene therapies, cell therapies, or regenerative medicines, scientific breakthroughs are spawning a growing number of emerging treatments that are eagerly anticipated because of their potential to cure a wide range of conditions.[4] One-time treatments that are not true cures but that offer the potential to halt the progression of serious illnesses such as multiple sclerosis and cancer are also on the horizon. Regulatory pathways are evolving to facilitate the early approval of such transformative therapies, and there are high expectations that they will bring hope and miraculous advances to patients and families who have long suffered without adequate options.

Looming over the hopes that these treatments will prove transformative for patients are concerns that their extreme costs will not be sustainable.[5,6] The first cell and gene therapies approved in the US have been priced between $373,000 and $2.1 million dollars for single treatments. In the short term there are already reports of employers and other plan sponsors who have decided to exclude coverage of gene therapies entirely from the health benefits they offer due to perceived budget-busting consequences of even a limited number of individual cases.[7] The long-term presents a broader concern that the aggregate cost of a rising tide of cures and transformative treatments will severely strain the overall affordability of health care for all insurers, both public and private. The stakes for patients and health systems are high. For all stakeholders it will be critical that methods for assessing evidence on these treatments and for translating it into pricing and payment mechanisms are ready for the challenge.

To date, policy analyses of cell and gene therapies have focused mainly on developing new ways to pay for one-time, extremely high-priced treatments by spreading the payment out over time in some form of installment approach.[5,8-10] If it were possible to implement this kind of new payment mechanism rapidly and broadly, the health system would gain an important tool to manage some of the concerns regarding uncertainty and short-term affordability of potential cures and similar one-time treatments. But the prospects for launching a radically new payment mechanism in the US health care system are dim, at least in the short-term, as the complexity of a multi-payer system imposes substantial barriers to the adoption of any long-term contracting platform linked to patient outcomes.[6] In its absence, the assessment and valuation of one-time transformative treatments, including the determination of fair value-based prices, will remain of central importance. And even should a new payment platform eventually emerge, this by itself will not be sufficient to address all concerns. For even if very high prices can be amortized over many years, and some form of retroactive discount or refund is given should treatment fail, the question remains: what is the fair value-based price to be used as the starting point for long-term payment plans?

Complex challenges in evaluating treatments for serious conditions, often among small patient populations, are nothing new. But is there something special about potential cures and other transformative treatments – or at least is there something special about some of them – that merits consideration of alternative assessment approaches?

This paper is the product of shared experience across health technology assessment (HTA) bodies in the evaluation of a range of transformative treatments, commissioned work examining a mock appraisal of a hypothetical CAR-T treatment,[11] a literature review, and a series of interviews with methods experts and stakeholders that began with a focus on whether "cures" required some kind of alternative assessment approach. From these sources, four particular issues commonly arose which we believe are the most potentially relevant in justifying alternative assessment approaches:

1) **Increased uncertainty with unrecoverable costs.** The available evidence at launch for potential cures will often be marked by extreme levels of uncertainty. Limitations in the evidence base will always include lack of long-term data and may be notable as well for a lack of experience with a novel mechanism of action and/or delivery and a lack of understanding of the natural history of the condition. These limitations will be made even more consequential if the evidence base consists solely of unrandomized clinical trials. This high level of evidentiary uncertainty is common to many treatments for serious rare diseases, but its impact on assessments and recommendations for fair pricing becomes distinctively challenging when payers must pay the entire cost of treatment upfront and will therefore face the possibility of huge unrecoverable costs should the treatment not prove to be as effective as hoped.
2) **Questions regarding additional dimensions of value.** Some methods experts and stakeholders argue that transformative treatments, and especially cures, offer distinctive advantages over traditional treatments arising from additional dimensions of value for treated patients and society that are not captured in traditional cost-effectiveness analyses.
3) **Time divergence between costs and benefits.** The time divergence between short-term spending and long-term health benefits accentuates questions about appropriate discounting rates in economic models.
4) **Affordability and fair sharing of economic surplus.** Transformative treatments offer the potential for magnitudes of health gain and/or cost offset that raise concerns that traditional cost-effectiveness methods will allocate too much of the economic surplus to innovators and will assign fair prices to transformative treatments that are manifestly unaffordable in the near term. This concern is amplified by the fact that many transformative treatments will not follow a traditional pathway toward generic competition following the end of exclusivity, thus shifting the long-term balance of economic surplus gained in favor of innovators.

This paper will explore the arguments for and against various alternative methods to address these four issues. It should be noted at the outset, however, that there are strong arguments that standard methods of HTA, including the suite of methods used to evaluate comparative clinical effectiveness and to analyze of long-term cost-effectiveness, are fully capable of evaluating potential cures and other transformative treatments. Confidence in current methods arises in part from the fact that these four issues present challenges that are largely similar in nature, if not in degree, to those of many treatments for serious, rare conditions.[12] Methodologists and HTA bodies have adopted various approaches to address these challenges in the past, and some may feel that these evaluation pathways and methods are already able to manage the increased uncertainty and all the other features that may seem, on the surface, unique to potential cures and other transformative treatments.

Another line of argument holds that there is only one real distinctive challenge presented by transformative treatments: the requirement to pay an extremely high price in the short-term despite substantial uncertainty about the long-term benefits. If this is the only problem, then there is an obvious fix: an outcomes-based installment payment plan in which the payer and the innovator can share in the risk that the treatment is not as effective as hoped.

But as stated earlier, rapid adoption of long-term outcomes-based payment schemes seems unlikely, at least in the US, and some stakeholders feel strongly that the underlying assessment of potential cures needed to support those arrangements still represents a special case needing new methods. Given the prospects for increasing numbers of cell and gene therapies and other forms of transformative treatments, it seems reasonable to analyze some of these arguments. Evaluating the rationale for different approaches, and the conceptual and practical dimensions of potential alternative methods, is an important step in making sure that assessment methods are fully ready to evaluate the coming wave of transformative treatments in support of an innovative, sustainable health insurance system.

1.2 Cures, Potential Cures, and Transformative Therapies

The preliminary focus of this effort was to consider methodological alternatives for the assessment of “cures.” Various attempts to define the term cure or “potential cure” have shown that there are divergent views on whether cures must be one-time treatments, must restore patients to full health, must lead to the total eradication of the disease/condition, and/or must require no on-going ancillary treatment.[5,13-17] Commentators and stakeholders are also divided on how long it is necessary to wait before declaring a treatment is a cure versus a potential cure.

Determining a single definition of a “cure” or “potential cure” will therefore not find easy consensus. As this project evolved it became clear that it would be necessary to decide which characteristics of a new treatment – whether it is a cure or not -- might raise distinctive evaluation

or pricing challenges such that alternative assessment methods should be considered. To that end, we propose that the four specific challenges for evaluation described earlier in this paper should be considered salient in the assessment of treatments that we will call "single or short-term transformative therapies," or SSTs.

We define SSTs as *therapies delivered through a single intervention or a short-term course of treatment that demonstrate a significant potential for substantial and sustained health benefits extending throughout patients' lifetimes*. SSTs include two subcategories:

- *Cures* that can eradicate a disease or condition; and
- *Transformative therapies* that can produce sustained major health gains or halt the progression of significant illnesses

There are several key features and consequences of this definitional approach. First, we narrow the field by specifying that special assessment methods may be needed only when a cure or transformative therapy is delivered as a single or short-term treatment. We believe it is the time divergence between short-term treatment and potential long-term benefits that creates the most distinctive characteristic of treatments for which alternative evaluation methods should be considered. As noted earlier, since the entire cost for the therapy may need to be borne at the outset, while the benefits accrue throughout the patients' lifetime, the impact of uncertainty about long-term clinical outcomes is greatly magnified for health system decision-makers. The time divergence between cost and benefit also invites greater questions regarding whether the standard approach to discounting rates in economic models of these treatments remains appropriate. Lastly, the benefits of single-time or short-term therapies that may provide substantial health gains and/or cost offsets over the long-term will be condensed by traditional cost-effectiveness methods into a single recommended price that may be neither fair nor affordable. Cures and other transformative therapies that are provided over the long-term raise none of these fundamental issues.

After narrowing the scope of consideration to single or short-term therapies, however, we believe it is reasonable to have broad criteria that allow special consideration both for transformative therapies that may not be considered true cures. It seems reasonable that a single-time therapy that produces a transformative health gain, e.g. from being ventilated and immobile to fully ambulatory, will generate the same evidence assessment and valuation challenges as do cures that fully eradicate an illness. Similarly, if a single-time treatment can halt the progression of a serious illness such as ALS or MS – for the rest of the patient's lifetime – the key issues related to assessment challenges would seem to apply equally.

As a corollary to this definitional approach, we do not believe that every gene therapy, cell therapy, or regenerative medicine should require consideration of alternative assessment methods. If they are delivered over time as daily, monthly, or even yearly treatments, standard assessment methods should be sufficient, although there may be some questions about additional elements of value that

are not fully captured in an economic model. In addition, not all cell and gene therapies will offer a *significant* potential for substantial and sustained benefits throughout the rest of patients' lives. For example, we know already that some of the gene therapies in development will modulate the effectiveness of other treatments and are not expected to produce transformative outcomes.[6] For the purposes of this paper, therefore, we will address the options for alternative assessment methods in their application to SSTs as we have defined them above.

1.3 Purpose and Methods Overview

This paper is intended as a technical brief on the four issues described above that may be viewed as potentially distinctive in nature or dimension as part of the assessment of SSTs.

ICER has previously authored a white paper on gene therapy that analyzed assessment challenges and explored the potential for innovative payment mechanisms to manage the tension between high prices and payers' need to maintain affordability.[6] ICER staff have also completed reviews of the first two CAR-T therapies, of the gene therapy Luxturna for a form of childhood blindness, and of Zolgensma, a gene therapy for spinal muscular atrophy. This experience has given ICER important perspectives on the challenges of assessing potential cures. Our partners in this project, NICE and CADTH, have provided extensive input based on their own experience and considerations of methods options for cell and gene therapies.[11,18] To complement the existing perspectives of the three HTA organizations, we also performed a series of interviews with leading health economics methods experts in the US and internationally, and we spoke with experts from the patient community and in the life science and insurance industries. Information on the individuals interviewed is available in Appendix A.

Along with these interviews, we performed a systematic literature review to seek articles suggesting or evaluating alternative methods for the evaluation and pricing of cell and gene therapies and other potential cures. The methods and results of this systematic review are described in a subsequent section of this paper, and the technical details of the literature search are provided in Appendix B.

Having digested the results of these interviews and of the systematic review, we created a template of potential methods adaptations for potential cures and from this broad menu selected a prioritized list of methods options to explore further (see Appendix C). We have analyzed these prioritized methods options qualitatively for their special relevance for potential cures, and, when possible, tested them quantitatively by applying them in modified economic modeling exercises for three different treatments that reflect varying "cure scenarios."

In this paper we discuss the set of potential alternative methods and present the findings of the empirical analyses we have done to test their impact. We describe the impact of different methods

on the incremental cost-effectiveness ratios for each treatment, discuss issues of face validity and potential usefulness for decision-makers, and present other lessons learned. These empirical results complement the conceptual analysis provided in other sections of the paper. The overall goal is not to present specific recommendations for methodological changes to current standard assessment approaches for ICER or other HTA bodies. Instead, we hope to provide an analytic foundation to support further discussion among all stakeholders.

2. Methods

A literature review was conducted to address the four key methodologic challenges presented by SSTs. To supplement the findings of the literature review, we also conducted interviews of methods experts and key stakeholders, both in the US and internationally.

2.1 Data Sources and Searches

For the literature review, we searched MEDLINE, EMBASE, Health Technology Assessment (HTA) Database, NHS Economic Evaluation Database (NHS EED), and the Cost Effectiveness Analysis (CEA) Registry for English-language publications published from December 2004 through February 2019 with key words related to cures, cell and gene therapy, and/or regenerative medicine. To supplement the database search, we performed manual checks of the reference lists of studies and interviewed key stakeholders with the aim of identifying any unpublished studies. We also supplemented our review of published studies with relevant data from conference proceedings. Overall, we identified 1,891 potential references, of which 56 met our criteria for qualitative review. The search strategies and other details of the literature review are presented in Appendix B.

2.2 Expert Interviews and Public Input

We conducted a total of 19 separate interviews with different experts. Among those interviewed were health economists and experts in HTA domestically and internationally, and, as noted earlier, we worked in depth with staff at NICE in the UK and CADTH in Canada to share experience, perspectives, and ideas for alternatives assessment methods. We also interviewed life science companies as well as relevant patient groups and payer organizations. Among all interviewees there were representatives from:

- Internationally recognized health economists from the US, Canada, and the UK (8)
- International health technology assessment organizations (3)
- US-based patient organizations focused on promoting cures, supporting patient communities with rare diseases, or within patient populations with SSTs near approval (3)
- US-based pharmaceutical companies and biotechnology organizations with SSTs in their research and development portfolios (2)
- US-based health plan (1)
- Trade organizations that support companies with a focus on cell and gene therapies (2)

Finally, we held a four-week open input period to solicit comment from interested stakeholders on methodological adaptations for SSTs. We received input from 24 organizations, including life science companies, health economic professional organizations, consulting companies, and patient organizations. A summary table of comments received is included in Appendix A.

3. Key Challenges in the Assessment and Value-Based Pricing of Single and Short-Term Transformative Therapies

3.1 Increased Uncertainty with Unrecoverable Costs

Previous authors have described multiple factors that often lead to important limitations in the evidence base for cell and gene therapies. These limitations present common evidentiary challenges for many treatments for serious, and often rare, conditions, and lead to greater uncertainty in the long-term comparative clinical effectiveness and cost-effectiveness of these treatments than is present at launch for most others.[6,11,19 20] SSTs are therefore a subset of therapies for which the evidence at the time of regulatory approval is marked by substantial uncertainty because of the following factors:

- Limited understanding of the natural history of the full spectrum of the disease
- Novel mechanisms of action and of treatment delivery techniques that may present new long-term safety concerns
- Small populations and serious, progressive symptoms that can make RCTs difficult or infeasible, often leading to reliance on single-arm trials whose results are more vulnerable to unknown biases
- Limited time of follow-up, leaving significant uncertainty about longer-term safety and the durability of treatment effect
- Lack of standardized patient-centered outcome measures or validated surrogate measures
- Lack of standardization of "usual supportive care" that often serves as the primary historical comparator or as the control arm in RCTs
- Variation in the risks and benefits of a therapy due to how it is delivered and, if relevant, the skill of the interventional provider

It is important to note that none of these elements that contribute to a high degree of uncertainty about long-term safety, clinical effectiveness, and cost-effectiveness are unique to SSTs. It is their frequent combination, linked to the possibility that upfront payment would result in huge unrecoverable costs, that raises questions regarding whether alternative methods are desirable for assessing, describing, or applying uncertainty within the assessment and appraisal frameworks for SSTs.

3.2 Questions Regarding Additional Dimensions of Value

Active debate continues on whether there are important unmeasured dimensions of value that should be systematically considered in the evaluation of all new therapies.[21] For example, ISPOR's white paper on value assessment frameworks suggests that there are reasons to consider multiple additional dimensions of value, including real option value, the value of hope, and insurance value – none of which may be captured fully by the standard QALY.[21] Other additional dimensions of value may be particularly relevant or even unique to SSTs. For example, it has been suggested that there may be intrinsic psychological benefits that are not captured in the QALY of feeling "cured" of a lifelong illness.[22] The ISPOR paper recognizes, however, as did the recommendations of the Second Panel on Cost-Effectiveness, that these additional elements of value remain controversial, and methods for empirically integrating them into cost-effectiveness assessments are not well established.[23,24] There are also intrinsic equity concerns about adding dimensions of value that only increase the assessed value of some forms of treatment -- and thus would support higher prices for them -- without creating some mechanism for balancing this with the resultant opportunity cost and attendant health losses due to other treatments foregone. Below we discuss the additional dimensions of value that we believe have the greatest chance of being most salient to SSTs and therefore raise the greatest questions about whether they should be incorporated as part of an alternative assessment methodology.

In the work performed under the auspices of the ISPOR Special Task Force on Value Frameworks, Lakdawalla et al. highlighted eight additional elements of value that are not captured by the standard QALY.[21] These elements of value include reduction in uncertainty, fear of contagion, insurance value, severity of disease, value of hope, real option value, equity, and scientific spillovers. After consideration of this literature and input from public comment and focused interviews, we determined that four of these potential additional dimensions of value could be particularly relevant to assessments of the value of SSTs: 1) value of hope; 2) insurance value; 3) scientific spillovers; and 4) real option value. We describe each of these in turn below.

Value of hope refers to the notion that many severely ill patients may wish to select a treatment that provides lower overall QALYs on average (e.g. due to an increased risk of early death from a risky procedure) if that treatment offers a greater chance for extended survival or a small chance of a cure.[21] In contrast to this preference from what may be called "risk-taking" patients, risk-averse patients may prefer to avoid short-term risk by preferring a treatment with more certain short-term survival benefits.

We believe that naming this dimension of value the value of "hope" is unfortunate and misleading. It conflates two things: the potential for a treatment to offer an added benefit by providing a distinctive spectrum or timing of risks and benefits; and the "hope" held by essentially all patients with a life threatening condition that some treatment might be found that can offer a glimmer of a chance of benefit for them, even if that chance is vanishingly small. We therefore believe that the

dimension of value labeled "value of hope" would be usefully renamed the "value of having the *choice* among treatments with a different balance and timing of risks and benefits." Not as succinct as value of hope, but far less likely to be misconstrued and misapplied in discussions regarding the potential benefits of SSTs.

The value of having choice of among treatments with different clinical profiles is not unique to SSTs but may find its most extreme relevance among patients who want to accept an increased short-term risk of death for a chance at a cure. To be clear, a claim for additional benefit of this type does not imply that it trumps all other considerations and would justify the use of any treatment that offered a small chance of long-term benefit. But this additional dimension of value may apply as a factor in broader deliberations on the value of certain SSTs that have, as per our definition, a *significant* potential of substantial and sustained benefits. The methods to measure this dimension of value empirically, however, are not well established. One complexity is that the value in having access to therapies with different clinical profiles is likely widely variable across individual patients and across conditions according to their severity and the nature of the differences between the clinical profile of specific drugs. Attempting to add an empirical weighting for this dimension of value at the population level therefore appears to be premature. In addition, as with other value domains, any empirical addition would still need to be considered in conjunction with some action to address opportunity cost concerns.

Insurance value is conceived of as the additional value of protection from future physical and financial risk gained by healthy individuals within the insurance pool who participate in paying for treatments through their ongoing insurance premiums.[21] It is argued that insurance value gives additional peace of mind and may increase individuals' willingness to pay for insurance for almost all treatments, but particularly for insurance that would pay for expensive treatments for serious conditions. Based on prior research that focuses on the value of health technology in a healthy population, one way to quantify insurance value has been described by Lakdawalla et al.[21] Alternatively, one may choose to specify an explicit mathematical model of consumer utility maximization and use it to calculate an estimate of insurance value.[21] In this case, one needs to specify the model of utility itself and have access to the following parameters: 1) the per-period incremental cost of the medical technology in question, and 2) the per-period incremental health benefit of the technology.

Existing estimates suggest that accounting for insurance value would add up to 40% to 60% to the conventional value of morbidity improvements as measured by the QALY.[25] Calculating added value for mortality improvements presents more complexity, because the conventional economic model for the value of life implies that people are approximately risk neutral over changes in their life expectancy.[21]

The idea of insurance value overlaps significantly with considerations given to severity or burden of illness. It is also not clear that willingness to pay for "peace of mind" would not apply equally to

societal spending in areas other than health care, such as environmental protection, defense spending, or other areas that could represent the sources of resources drained to accommodate the opportunity cost for higher health care spending. One must ask what the broader impact would be of adding 40%-60% more to current expenditures for health care, the level of spending required to fully capture insurance value according to leading empirical estimates.

Scientific spillover effects refers to the potential for new treatment approaches to open up new lines of research and care that will produce as yet unknown future therapeutic advances for different and even unrelated conditions.[21] Economists have empirically documented the causal effect of early innovation on future breakthroughs using National Institutes of Health funding as a natural experiment and clinical trial starts as an outcome.[26]

However, many economists have noted that spillover effects can happen in other areas of social investment, such as education, and that estimating the likelihood that any specific new therapy will or will not lead to unforeseen future benefits is impossible.[21] Even if spillover effects were considered as likely, there are no methods for determining how much empirical weight to give this added value when considering a fair price. According additional value on the basis of possible scientific spillover effects also risks double reward. All subsequent innovations are able to receive the spillover benefit from the preceding innovator through the price they are able to charge. Moreover, many if not most innovators are themselves capitalizing on spillover effects from federally funded research. And, lastly, as must be repeated with any consideration of adding value domains to the assessment of SSTs, any addition raises the concern that unknown patients will suffer the opportunity cost health losses for decisions that accept new services at prices that exceed the incremental cost-effectiveness threshold for the health system.

***Real option* value** is related to the notion that patients face uncertainty about when and how future advances in medicine will occur.[21] Previous economics literature has identified real option value as an additional element of value that may be relevant for specific medical products.[27-29] Hypothetically, if a patient had to choose between two treatments offering the same expected QALY gain, they might prefer the one that offers the greater life expectancy (but lower quality of life), as this provides a greater chance to benefit from access to future scientific and clinical advances.[21] Previous research has estimated real option value by accounting for projected increases in survival using established forecasting models.[28,29]

Real option value is not relevant for therapies that are known cures but could be a consideration when assessing the value of a potential cure or a transformative treatment that halts a serious progressive illness. For a potential cure with promising short-term data, even if the therapy does not provide a long-term cure, a short extension of life that offers a chance at survival until a better treatment is available may be viewed as having greater value than its pure QALY estimate. Similarly, transformative treatments that may be able to halt a serious progressive illness offer the fsame added benefit.

The arguments against trying to include real option value as an added benefit for SSTs are both conceptual and practical. First, real option value could be considered as an added benefit of any life extending treatment, not just SSTs, so considerations of adding it as a factor in evaluation only of SSTs is problematic. As with other dimensions considered as potential added value, the opportunity cost problem exists equally for real option value. From a practical standpoint, there is very little work on how to empirically determine a weighting for real option value, and therefore it is difficult to assess its potential impact on assessments for SSTs.

Summary

Due to the severity of the conditions, and to the transformative "leap" in clinical benefits that may be available with SSTs, we believe that assessments of SSTs are likely to trigger enhanced consideration of several of these additional elements of value. However, as noted above, the methods for quantifying these dimensions of value remain exploratory and lack any consensus among academic health economists. That by itself would be a strong argument not to consider attempting to quantify them as part of the assessment of SSTs. Second, although we have argued that SSTs have distinctive characteristics that increase the relevance of some of these additional dimensions of value, SSTs are not truly unique in this sense, and incorporating additional value considerations for SSTs alone could be viewed as unfair to a broad range of other services.

A major overriding factor that would argue against the inclusion of additional value domains cannot be overstated: their inclusion would raise fundamental equity concerns. Higher spending on certain SSTs (or other treatments) that get extra credit for these additional value domains would lead to opportunity cost effects either inside or outside the health system. This concern could be addressed by creating a balanced scoring weight for each value domain that ascribes a "negative" weight to some services while giving SSTs a "positive" weight. Another way to balance out the additional spending related to higher value scores would be to lower the general cost-effectiveness threshold range used as a general guide to decision-making. As can be imagined, any method to accommodate higher value assessments with lower value assessments or a lower cost-effectiveness threshold would create winners and losers in the health system. It appears premature to contemplate any such methodological adaptation for SSTs in the near term.

Therefore, although SSTs seem likely to trigger enhanced consideration of these additional elements of value, qualitative methods for integrating them into decision-making may hold greater promise than do attempts to quantify them and add them to the QALY. Qualitative methods during deliberation are used by all HTA groups and decision-makers for dimensions of value that may not be adequately captured by the QALY, and continuing work with multi-criteria decision analysis (MCDA) may ultimately lead to improved methods to capture and weight these and other dimensions of value for all treatments, not just SSTs.[20,30]

3.3 Time Divergence between Costs and Benefits

Typically, individuals – and by extension, society – value future costs and effects less than current costs and effects, and the value of both diminish the more distant in the future they occur.[31] "Discounting" in economic evaluations in health care seeks to take into account this impact of time on how costs and outcomes are valued, assigning a percentage by which to lower the value of a cost or health outcome the further into the future it is realized.

Discounting is a standard method of economic modeling, although the choice of the discounting rate and whether costs and benefits should be discounted uniformly or in some differential way remains controversial.[32,33] In the US, the standard approach has been recently confirmed by the Second Panel on Cost-effectiveness in Health and Medicine: a uniform discount rate of 3% applied to both costs and benefits.[34,35] Other countries may use a different discount rate, ranging somewhere between 1.5% and 5%, but most, including the UK and Canada, also use a single discount rate for both costs and effects.[32] Four European countries, however, have moved to a differential discounting approach in which costs are discounted at a higher rate than effects. These countries have selected differential discounting because they favor the view of some economists that as time passes and societies grow wealthier, they value health benefits more than they do at present.[31] In part due to this reasoning, NICE recently introduced the option of considering differential discounting for public health interventions and in cases when therapies offer long-term health benefits.[31]

SSTs by their nature incur costs through a single or short-term intervention while providing potential health benefits not only immediately but over an extended time course. The long-term nature of benefits amplifies the importance of which discount rate is selected, and the time divergence between costs and benefits increases the relevance of questions about whether differential discounting should be considered. For both of these reasons it is important to explore the conceptual foundations of discounting as they apply to SSTs and understand the quantitative impact of using alternative discounting methods in the economic evaluation of these treatments.

3.4 Affordability and Fair Sharing of Economic Surplus

For conditions that appear in childhood and which are rapidly fatal, true cures could add 50, 60, or even 70 years of healthy life for all patients treated. An SST that generated 50 additional QALYs (before discounting) would have a value-based price of $5 million using a traditional societal willingness to pay threshold of $100,000 per additional QALY. It is likely, however, that many SSTs for chronic conditions will offer not only magnitudes of health gain rarely seen with other interventions but the additional promise of substantial cost offsets in the health system over the lifetime of patients, as the cumulative costs of many years of previously required care are avoided.

Thus, it has been noted that value-based prices suggested by traditional cost-effectiveness analysis could be in the range of $20-$25 million in the US context for cures of an expensive chronic condition such as hemophilia.[3,6] Even if all the health care services that are prevented by an SST were "repriced" at cost-effective levels, the magnitude of QALYs gained and cost offsets over a lifetime would lead to value-based prices far higher than the health system has ever seen before.

There are two interconnected methodological and policy issues related to this scenario. The first arises from allocation of economic surplus generated by an SST. One reason that traditional cost-effectiveness methods assign such a high price to an SST is because innovators are able to "price in" more of the future health gains and cost offsets into a single or short-term price than they would receive for a similar treatment paid over a period of time that would face generic competition after the expiration of the patent and the sunset of the exclusivity period.[36] Although HTA assessments generally do not factor in potential price reductions for a new treatment following the end of exclusivity, the general balance of the economic surplus retained by the innovator versus that retained by society is built upon an historical landscape in which the manufacturers of most treatments have been expected to retain most of the surplus during early pre-competition years, whereas society is expected to retain most of the surplus for many years thereafter once competition has driven the price down to marginal cost plus some minimal profit. SSTs, however, in part because they are likely to be cell or gene therapies that may not ever have a generic version, may face little competition from generic or biosimilar versions even after exclusivity ends, and therefore their upfront price may result in the innovator capturing all the economic surplus from the treatment in perpetuity.

The related policy issue to extremely high prices, even if they appear to be "value-based" by falling within the long-term cost-effectiveness thresholds, is that these prices could prove unaffordable in the short term. Although the number of SSTs that will enter clinical care in the next five years is difficult to estimate, it is possible that if some are for relatively large patient populations that the cumulative cost will be impossible to manage in the short-term without drastic cuts to other health services or rapid increases in insurance premiums that would represent too high an opportunity cost for society.

Of course, traditional cost-effectiveness methods are not "wrong" to calculate value-based price ranges at this level just because the prices are extremely high. And it is unlikely that innovators would seek to push pricing to levels that would lead to significant public backlash. But the recent history of the conflicts that have been triggered by climbing launch prices for orphan drugs suggests that HTA groups should explore ways to provide additional perspectives on how to calculate or assign economic surplus to recommendations for appropriate pricing when drugs have the potential to generate extremely high QALY gains and/or cost offsets.

4. Potential Alternative Assessment Methods

4.1 Increased Uncertainty with Unrecoverable Costs

After considering alternative methods that had been suggested in the literature, during interviews, or arising from HTA experience, we focused on six potential methods to address the heightened uncertainty in the long-term clinical and economic outcomes of SSTs. These methods are listed below in Table 4.1 .

Table 4.1. Potential Alternative Methods to Address Increased Uncertainty in Clinical and Economic Outcomes of SSTs

Potential Methods to Address Uncertainty
Adopt cure proportion modeling to model long-term outcomes
Average the results of multiple models that differ in their structure
Perform threshold analyses for cost-effectiveness at different time horizons
Use different assumptions about the durability of safety and effectiveness to develop three primary scenarios for decision-makers: base case, conservative, and optimistic
Use probabilistic sensitivity analysis to generate multiple simulations and apply a secondary requirement at any willingness to pay threshold that a high proportion of simulations are below a certain cost-effectiveness threshold
Use probabilistic sensitivity analysis to generate multiple simulations and apply a policy paradigm in which a certain magnitude of uncertainty is linked to a default recommendation for outcomes-based contracting with substantial financial stakes

4.1.1 Cure Proportion Modeling

Traditional survival analytic models rely on fitting parametric curves to Kaplan-Meier survival plots and using those curves to project survival. However, in cases where some proportion of patients can be considered cured, mortality risk may return to that of the background population while those patients who are not cured continue to have the disease-specific mortality risk. In such cases, traditional models may not adequately describe the heterogeneity of the population, may provide biased estimates of survival, and do not allow for direct estimation of the cure proportion.[37,38]

Cure proportion modeling techniques include mixture and non-mixture cure proportion models.[38] The cure proportion can also be estimated using flexible parametric survival modeling that utilizes splines to allow the survival function to change over time.[39] All of these cure models may offer specific advantages in modeling the long-term outcomes of SSTs, in that they allow for a heterogeneous population of cured patients (with background mortality rates) and non-cured patients (with additional disease-specific mortality risk). For example, in mixture cure models, these two populations are analyzed separately and combined using weighted averages for survival and costs. In such cases, using simple averages across the entire population would lead to biased estimates for survival and costs.[37,40]

Models that explicitly account for heterogeneity among patients receiving SSTs may produce quite different results from those that do not. For example, Othus et.al. analyzed ipilimumab and glycoprotein 100 treatments for patients with advanced melanoma, using a mixture cure model that assumed the study population is a mix of patients who are cured and patients who are not cured.[37] This model incorporated the heterogeneity associated with having cured patients in survival analysis, i.e., the cure proportion. Using mean overall survival from conventional (parametric) statistical analyses, the authors found an estimated difference in survival of eight months for ipilimumab over glycoprotein 100, but this did not adequately characterize the heterogeneity across cured and uncured patients. When taking the cure proportion into account, overall survival appeared to be similar for patients not considered cured (10 vs. 9 months for ipilimumab and glycoprotein 100, respectively) and for those considered cured (approximately 26 years for both arms). However, it was the proportion of patients considered cured that drove the overall survival difference, at 21% for ipilimumab and 6% for glycoprotein 100. Not accounting for the cured proportions led to an estimated cost-effectiveness ratio of $324,000 per QALY for ipilimumab compared to glycoprotein 100, while using a mixture cure model led to an estimated ratio of $113,000 per QALY.

Cure proportion models can reduce bias in survival and cost estimates by separately accounting for the survival and cost of the proportions of patients considered cured or not, and then combining them in a weighted average, rather than using mean values for the combined population. Such models also provide a more accurate characterization of variation within a population with differing responses to treatment and may provide a clearer picture of the drivers of differences between

treatments (e.g., the proportion cured vs. mean overall survival). Othus et al. conclude that "in situations in which treatments provide a proportion of patients with durable remissions from their illnesses, we believe that the mixture cure model approach may be superior to standard approaches in estimating incremental cost-effectiveness."[37]

The use of cure proportion models has increased in recent years and is expected to continue to gain in popularity as more SSTs are developed. However, cure models should only be considered when there are enough follow-up data to support evidence of a heterogeneous population with some long-term survivors, such as a survival curve that shows a clear plateau at some time point.[37] Ishak et al. have also noted the risks of using cure models with data that are not mature enough to exhibit the expected survival plateau, advising more conservative approaches for earlier projections of survival.[41] Also, accurate estimation of the proportion of patients cured at different time points is best calculated from patient-level data, which are not always available for HTA organizations, requiring the digitization of scanned Kaplan-Meier plots or similar methods.[42]

However, under certain assumptions, these and similar methods for modeling proportions of patients achieving a cure will be useful for the analysis of SSTs. In cases where there is a plausible hypothesis for a potential cure and where available data show evidence of a plateau in survival, these models are likely to better fit available survival data. By providing results that more accurately fit available survival data, cure proportion modeling can help reduce uncertainty for decision-makers. We will present the empirical results of applying cure proportion modeling and spline-based survival curve fitting in hypothetical cure scenarios in a later section of this paper.

4.1.2 Model averaging

Model averaging has been used by some health economists as a method to explore structural uncertainty in cost-effectiveness analyses.[43,44] Jackson et al. classify the different types of uncertainty in economic models as *judgment* uncertainty (i.e., what data sources to use), *parameter* uncertainty (i.e., what specific values to use as model inputs), and *model (or structural)* uncertainty (i.e., what model structure to use). While the first two types of uncertainty can be addressed by using various data sources and parameter values in scenario and probabilistic sensitivity analyses, model uncertainty is usually not addressed in a systematic way.

Model averaging involves developing models with different structures, assigning weights to models based on some measure of adequacy or fit (e.g., Akaike's information criterion) and then using weighted-average outputs across models as a way to capture the distribution of structural uncertainty while still providing a weighted average result for decision-makers. It provides a more formal way to weight the outputs across different models or scenarios using prior and posterior probabilities, rather than relying on subjective weights from decision-makers.

Jackson et al. developed an example using a Markov model of surgery for abdominal aortic aneurysm repair. This model produced substantially different estimates of the probability of cost-effectiveness in the base case and three different scenarios that used different structural assumptions about mortality and treatment effects. These scenarios showed a range of probability of being cost-effective at a £20,000 per QALY threshold from 0.011 (the base case) up to 0.52. Their model-averaged results across these scenarios showed that the intervention in this case was not likely to be cost-effective at a threshold of £20,000 per QALY (estimated probability of 0.069).[43]

The major limitation to model averaging is practical, as the characterization and development of several structurally differing models is likely to be both time- and resource-intensive. However, when HTA organizations and life science companies have differing opinions about the most plausible structure for a model and have the ability to run different structural models holding other parameter inputs equal, it could prove a useful way to explore the heightened uncertainty associated with many SSTs and allow decision-makers to assess the impact of different major assumptions on the cost-effectiveness results.

4.1.3 Analyses at different time horizons

When the price of an SST is known or has been formally proposed but there remains substantial uncertainty about the durability of its clinical benefits, a type of threshold analysis can be done to determine how long the benefits would have to last in order for the SST to meet a given cost-effectiveness range. As a hypothetical example, consider a new SST that appears to be a potential cure for some or all patients, but for which there are no outcomes data on patients more than two years after treatment. A threshold analysis could be performed, using the existing price, to determine exactly how many years beyond 2 years the drug would need to remain 100% effective (and in what proportion of patients treated) in order for the drug to meet a cost-effectiveness threshold of $100,000 per QALY. If the analysis suggested that the drug would need to remain 100% effective in all patients for a minimum of 10 years to meet this threshold, decision-makers could then apply their best judgment regarding whether it was likely that the drug would remain effective for that duration of time or not.

For SSTs that are transformative therapies but not cures, similar threshold analyses could be done to determine what level of benefit would need to continue at different time horizons in order for the SST to be considered a reasonable value at its given price. This general approach is only applicable, however, when there is a known price for the SST. In addition, durability of benefit will rarely be the only major uncertainty about which decision-makers will be concerned. We describe an option below in which broader conservative and optimistic scenarios are constructed to complement the base case, an approach that may offer a more flexible and comprehensive way to operationalize the basic idea of providing decision-makers with information on how long a treatment's short-term results would need to project into the future for it to merit its current – or proposed – price.

4.1.4 Conservative and optimistic scenario analyses

HTA assessments that involve cost-effectiveness often present decision-making bodies with multiple different sensitivity and scenario analyses. Sensitivity analyses are frequently run to demonstrate the impact of varying one or more inputs into the model, such as an assumption about the quality of life related to a particular health state. The distinction between sensitivity analyses and scenario analyses is not always clear, but in many cases the term scenario analysis is used to imply a more substantial shift from the base case approach, such as using a different overall perspective (e.g. societal vs. health system), a different age cohort, or a different time horizon.

Given the substantial uncertainty that often accompanies early assessments of SSTs, one approach that can be considered to give additional perspective for decision-making is to provide a sense of how widely variable the results are when the results generated by the base case modeling assumptions are compared to those when the model is populated with broadly "optimistic" assumptions, and the results of the model when "conservative" assumptions are used instead.

Indeed, good deliberation on the results of any cost-effectiveness model should include an attempt to understand how variable the results are under different sets of assumptions, and HTA reports and deliberative processes regularly encourage this approach. For HTA bodies that accept model submissions from life science companies, it is routine to consider the initial company submission as implicitly optimistic, with outside economist consultants often providing a more pessimistic recommendation for the base case, and the deliberative process empowered to seek from between these options a judgment of the most plausible base case for decision-making. But for HTA bodies that develop their own models or commission them from outside academic collaborators, it may be helpful to consider formalizing a more systematic approach to providing three specific sets of results for SSTs (and possibly all treatments) in a way that fosters a more explicit and transparent consideration of the role of uncertainty in final policy decisions.

To this end, one option would be to present what could be considered "best-case" and "worst-case scenarios." This approach would consistently use the most extreme (yet not impossible) parameter inputs and other assumptions across the entire model to characterize two polar ends of the spectrum of potential cost-effectiveness results. While this would show the full potential range of outcomes, the accumulation of inputs and assumptions all tilted toward one end of the spectrum would be extremely unlikely to occur in the real world, and therefore might prove more misleading to decision-makers than helpful.

A more promising approach would be to complement the base case results with results generated by "plausible" optimistic and conservative scenarios. One major challenge in this approach is that it requires considerable judgment in how to select and set variables and other assumptions in the two complementary scenarios. HTA groups and collaborating modelers will have an inherent bias to support their own base case modeling assumptions; life science companies will have an inherent

bias to support alternative scenarios (i.e. optimistic scenarios) that generate more favorable cost-effectiveness findings for their product. There could be an infinite number of minor modulations to the parameter inputs and assumptions in any model that could be considered, and so any judgment about which to change and to what extent in the creation of two major alternative scenarios may appear capricious and will certainly be contested.

To explore this methods option further, we will present empirical results of a three-scenario approach to hypothetical cures in a later section of this paper.

4.1.5 Probabilistic sensitivity analysis and linkage to a secondary "uncertainty" criterion

Probabilistic sensitivity analyses and their representation via cost-effectiveness acceptability curves are standard methods used to explore uncertainty in modeling results and present the results to decision-makers. The goal of these techniques is to help inform understanding of the relative robustness of the results to variation across all possible inputs to the model.[45,46] Some HTA groups and decision-makers have expressed the view that when uncertainty about clinical and cost-effectiveness is substantially greater than usual, the most relevant cost-effectiveness threshold for decision-making should be lower to lessen the risk of allocating resources to a treatment that does not achieve the anticipated benefits. In this view, greater uncertainty increases the risk of wasteful spending and therefore should only be contemplated when the most plausible cost-effectiveness ratio is lower than the standard threshold.

Although this approach to decision-making is acknowledged conceptually by many, we are aware of only one decision-maker that has proposed an explicit quantitative approach to link the level of uncertainty to a reduction in the cost-effectiveness threshold for decision-making. The Joint Committee on Vaccination and Immunization (JCVI), an independent expert advisory committee of the United Kingdom Department of Health, has proposed to link the results of probabilistic sensitivity analysis to the base case results by stipulating that positive funding decisions for vaccines should only be taken when not only the base case incremental cost-effectiveness ratio is below the standard £30,000 threshold but 95% of scenarios in a Monte Carlo simulation are also below that level.[47] Although this specific mechanism has been formally proposed, it is not clear yet whether it has been put into practice.

Conceptually, although one could argue that such an approach should be equally applicable to any new treatment, the greater uncertainty expected with most SSTs makes consideration of a secondary cost-effectiveness criterion linked to PSA results particularly salient. There is, however, no principled way to decide how to select the specific parameters of this kind of uncertainty criterion. Should decision-makers require 95% of simulations to be below a certain threshold, or only 50%? Should the threshold used for the uncertainty criterion be the same as for general cost-effectiveness, or somewhat higher? These decisions will need to reflect the relative risk attitudes of decision-makers and may vary across different SSTs depending on the magnitude of their QALY

gains, the primary drivers of uncertainty, and/or the potential budget impact. But the instinct of decision-makers to apply a lower effective cost-effectiveness threshold in cases of heightened uncertainty leads us to believe that it will be valuable to explore the empirical impact of this approach applied to different cure scenarios.

4.1.6 Probabilistic sensitivity analysis and a secondary policy requirement for outcomes-based payment

To guide decision-making, probabilistic sensitivity analysis and its presentation through cost-effectiveness acceptability curves could also be linked not to a separate uncertainty criterion but to a policy pathway that would link positive funding decisions to requirements for payment mechanisms to share risk between the innovator and the payer. The general idea of managing uncertainty by implementing outcomes-based contracts has become popular among both life science companies and payers, and the number of these agreements has been growing in the US and internationally.[48,49] Although they have been viewed primarily as optional mechanisms that would be considered on a case-by-case basis, it is possible to imagine that a specified pathway could be created that would mandate that funding for an SST for which there was a high level of uncertainty could be provided only under conditions of an outcomes-based contract.

There are many elements of this potential approach that would raise important questions. First, would outcomes-based contracts be required for all SSTs or only those with a certain level of uncertainty and/or anticipated budget impact? If a level of uncertainty is used as a criterion, it is possible that it could be structured along the lines used by the JCVI in the UK as described above, i.e. that if the PSA revealed that >5% of simulations produced cost-effectiveness ratios above the upper threshold, then an outcomes-based contract would be required for funding. But the selection of the relative amount of uncertainty that would trigger such a requirement would be arbitrary and might need to vary depending on contextual factors.

Second, even if a policy pathway were developed for SSTs demonstrating a given level of uncertainty, it is unclear how to determine the magnitude of the risk that should be borne by the innovator as opposed to the payer. The complexities of outcomes-based contracts begin with determining the amount of money at risk, but also include difficulties in agreeing on suitable outcomes measures, procedures for reconciliation, etc. It is possible that some third-party could be assigned the task of mediating between payers and companies to address all these issues and issue a recommended outcomes-based contract, but to set this up as a requirement for funding would raise many conceptual and practical dilemmas that could be extremely difficult to address in a transparent, reliable fashion.

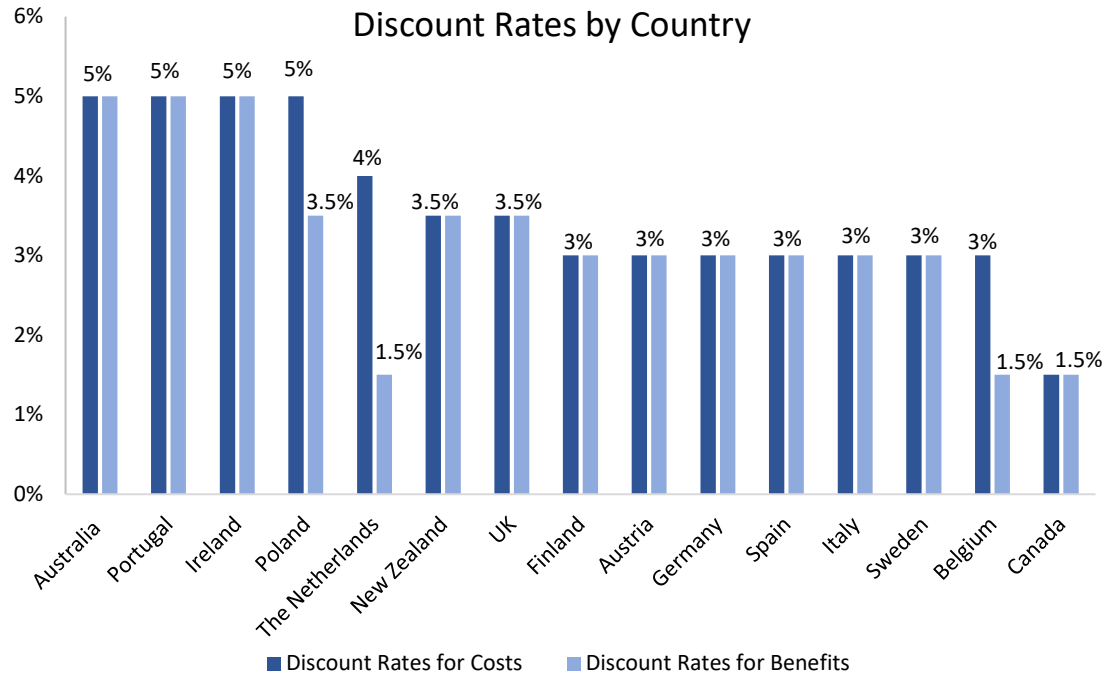
4.2 Time divergence between costs and benefits

Current International Approaches to Discounting

As noted earlier, HTA agencies around the world apply an annual discount rate of between 3% and 5% for costs and between 1.5% and 5% for health benefits.[50] Twelve HTA agencies (Australia, New Zealand, Finland, Portugal, Canada, Austria, Germany, Spain, UK, Italy, Sweden, Ireland) apply uniform discounting for costs and benefits,[51-62] while four HTA bodies (Poland, Belgium, Russia, and the Netherlands) specify higher discount rates for costs than health benefits (see Figure 4.1 below).[61-63] In England, there is some flexibility in the NICE process when "… treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years)…." In such cases a non-reference case discount rate of 1.5% for costs and outcomes may be considered by the Appraisal Committee *if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved*.[52]

Many agencies require the standard discount rate to be varied in sensitivity analyses to examine the sensitivity of the results to the discount rate. In Sweden, recommendations suggest that sensitivity analysis should include use of discount rates of 0% and 5%, as well as a calculation where costs are discounted by 3% and health effects by 0%.[54]

Figure 4.1. Guidelines on Discounting in Selected Countries



Methods to Determine Uniform Discount Rate Level

Uniform discounting, which remains the most commonly used discounting method,[64] is supported by two main arguments: 1) the consistency thesis, which proposes that inconsistencies may occur by discounting at two different rates when defining preferences for health-care programs with costs and health outcomes occurring at different moments in time;[65] and 2) the postponement paradox, where Keeler and Cretin argue that if health benefits are discounted at a lower rate than costs, the cost-effectiveness ratio can be improved by delaying the introduction of the technology in question and could continue to be improved by further delays *ad infinitum*.[66]

In the United States, the 2nd Panel of Cost-Effectiveness in Health and Medicine has recommended a 3% rate for both costs and outcomes.[35] This rate is based on estimates of the real consumption rate of interest and data on real economic growth, which are thought to reflect the social rate of time preference. The Panel also called for sensitivity analysis of discount rates, as well as additional research into the use of different discount rates. However, Paulden et al. have critiqued the Panel's rationale as departing from recent literature on how discount rates may vary for different perspectives or types of health care budget (e.g., whether constrained or not), as well as discussing recent arguments for differential discounting.[32]

Most other countries have used a similar rationale (the real interest rate) to select a single discount rate for both costs and benefits, although the specific rate may vary, with 3% and 5% being the most commonly used.[31] Another justification for the use of a specific discount rate, such as 3%, is to allow for consistent comparisons across different or prior evaluations.[31,35] Other countries, such as the Netherlands, have chosen to use differential discount rates for costs and effects, as discussed below.[31]

Differential Discount Rates

As noted earlier, the wide divergence in time between the early costs and the long-term potential benefits of SSTs has increased interest, particularly among the life science industry and some patient groups, in exploring differential discount rates for costs and benefits in economic assessments. The rationale for differential discounting is supported by empirical studies demonstrating greater positive time preference for health than for money.[67] Gravelle and Smith showed that the monetary value of health effects is expected to grow over time, and argue that this growth needs to be accounted for in economic evaluations.[68] When health effects are valued monetarily, this can be performed by using a growing monetary value for health. When non-monetary quantities are used, such as QALYs, the growth can be accounted for by lowering the discount rate for health effects relative to that of costs—that is, differential discounting.

Claxton et al. have also demonstrated that if the budget for health care is fixed and funding decisions are based on incremental cost-effectiveness ratios, then discounting costs and health gains at the same rate is correct only if the threshold remains constant.[69] They also showed that expected growth in the consumption value of health does not in itself justify differential rates, but implies a lower rate for both. The authors therefore draw attention to whether the social objective is to maximize discounted health outcomes or the present consumption value of health; on whether the budget for health care is fixed; on the expected growth in the cost-effectiveness threshold; and on the expected growth in the consumption value of health.[31]

Summary

There are strongly held opinions among health economists and HTA bodies on whether uniform or differential discounting is most appropriate for all treatments. Most HTA agencies have opted for uniform discount rates, and only one (NICE) has suggested possible criteria for an exception for therapies that have many of the features of SSTs. In a later section of this paper we will present empirical results of applying different discounting approaches to various cure scenarios.

4.3 Affordability and fair sharing of economic surplus

As described earlier, many SSTs are likely to offer the promise of health gains far greater than most new drugs, and SSTs for chronic conditions may also produce substantial cost offsets in the health system over the lifetime of patients, as the cumulative costs of many years of previously required care are avoided. Traditional cost-effectiveness methods will translate these enormous potential health gains and cost offsets into pricing levels that represent a much greater capture of the economic surplus provided by the treatment than would be the case were the same treatment provided and reimbursed in a chronic fashion. [70] These prices are likely to be viewed as unfair and in the aggregate may create unacceptable opportunity costs within the health budget or between health and other desirable social spending.[71]

Price caps linked to short-term budget impact

One fairly straightforward way to manage "value-based" pricing that creates affordability challenges is to cap any value-based price at a level that fits within an explicit or implicit budget impact threshold. ICER's standard assessment methodology includes an analysis of the potential budget impact over 5 years for all new treatments, and we calculate on an annual basis a threshold for anticipated budget impact that would represent an overall cost to the system in an initial 5-year period that would contribute to a rise in overall health care spending significantly faster than the national economy is expected to grow. When the target uptake for a new drug multiplied by its real-world price would exceed this threshold, ICER includes in its final reports an "affordability and access alert" for policymakers.[72] Anecdotal feedback from payers and policymakers has been strongly favorable to this approach, although it is generalized to national uptake figures and therefore has limited applicability to any particular payer in the diverse US health system.

Despite the integration of considerations on short-term affordability into ICER's assessment reports, we keep long-term cost-effectiveness and short-term affordability distinguished as separate concepts and do not use affordability estimates directly to modulate the suggested value-based price benchmark in our reports. These price benchmarks remain based solely on standard cost-effectiveness approaches. It is therefore obvious that one option to address concerns about SSTs whose value-based pricing would raise affordability concerns would be to use budget impact analysis explicitly to set a cap on price recommendations. This approach would be relatively easy to implement, but doing so would be likely to penalize treatments that happen to be SSTs as opposed to treatments that are taken over time, shifting the incentives for innovators toward chronic treatments and away from the kinds of SSTs that patients and society would value more. Therefore, we believe that simple budget impact caps as a solution to value-based prices that are "too high" should not be a preferred potential alternative method for the derivation of recommended prices for SSTs.

Shared Savings Approaches

Other than budget impact caps, we found little conceptual or empirical work in the health economics literature exploring options to provide alternatives to extremely high value-based price estimates that could be generated from assessments of some SSTs. Recently, Drummond and Towse have proposed consideration of "rate of return" pricing when value-based pricing produces results that are either too low (e.g. for some ultra-orphan drugs) or too high (for potential cures).[73] This idea merits further consideration but remains exploratory and would require contribution of closely guarded development cost information from individual life science companies.

One idea introduced by Pearson and colleagues at ICER is the concept of a "shared savings" approach that would split, in some proportion, the value of substantial cost offsets generated by SSTs for expensive chronic conditions.[74] Using this approach, innovators would get some, but not all, the economic surplus arising from an SST. Shared savings applied to cost offsets would not address the pricing of large QALY gains expected from many SSTs and would leave the rewards for health gains intact. The economic surplus due to QALY gains from SSTs could also be shared differently between innovators and society, but we believe that a focus on sharing cost offsets may appeal more to policymakers as a solution to the most egregious prices that would otherwise be recommended by traditional cost-effectiveness methods.

The reason a focus on cost offsets may receive more policy maker approval in the US arises from the history of contracting in the US between insurers and health care providers. The term "shared savings" came into common use in the US many years ago as a contractual approach between insurers and health care providers that would split in some pre-ordained proportion any savings achieved from improved efficiencies in care. The goal was to align incentives for controlling costs while ensuring high quality performance.

If transferred over to payment for SSTs, it is clear that the key question underlying this approach is how to determine what percentage of estimated cost offsets should be assigned by the model to the SST (innovator), and which to the payer. Unfortunately, there is no obvious normative answer to this question. There is no empiric way to determine the most appropriate split; it is a value judgment based on views of what levels of return on investment are adequate to reward innovation

, among other factors.

We suggest, however, that there are two different approaches to setting a shared savings level that can be considered. The first is to set the default arbitrarily at a level such as 50%, with certain criteria that can be applied to create a sliding scale to decide the relative proportion for each party. For example, these criteria could include 1) the magnitude of governmental investment in the basic science underlying the cure has been substantial; 2) the innovator's own research and development costs; 3) whether the cure will potentially eradicate a disease, thus limiting future returns on

investment (e.g. a cure for HIV), or whether there will always be a recurring incident population born with the condition; and 4) the potential budget impact based on the size of the patient population. These criteria could be used to suggest whether the proportion of cost-offsets in an economic model being assigned to the value-based price of an SST should be relatively higher or lower, even if there remains no explicit way to determine exactly what that split should be.

Another conceptual approach is to model shared savings by creating a hypothetical patent and exclusivity cliff at a time point after launch at which the share of the economic surplus shifts from the innovator to the health system.[75] This approach would directly try to account for one of the key differences related to SSTs: that they are unlikely to face generic/biosimilar competition and can therefore capture much more of the economic surplus in an initial value-based price than they would receive if the price were subject to competition in later years of chronic treatment.

It is hard to estimate an "average" length of time before a new drug receives generic/biosimilar competition. Patents last for 20 years but are subject to extension; exclusivity is granted by the FDA for five years from the time of NDA approval for most new drugs and seven years for orphan drugs. After benchmarking with analysts in the NHS, we have chosen to examine a shared savings approach in which cost offsets are included in a drug's price only until a patent-exclusivity cliff at 12 years as a rough average of the length of patent and/or exclusivity time expected before generics are both allowed and have reached the market.[76-80] From that time point our shared savings model will assign all the economic surplus arising from cost offsets to the health system as a way of trying to recreate the original underlying expectation that monopoly pricing will capture all the economic surplus up to the cost-effectiveness threshold prior to competition, but that there will occur a shift when the time point is reached at which competition brings prices down and the health system begins to capture more of the economic surplus.

5. Empirical Analyses of Selected Alternative Methods

5.1 Overview

We analyzed prioritized methods options suggested by our literature review, interviews, and input from other HTA bodies by applying them in modified economic modeling exercises for three different treatments that reflect varying SST scenarios. We describe here the impact of different methods on the incremental cost-effectiveness ratios and associated value-based prices for each treatment, discuss issues of face validity and potential usefulness for decision-makers, and present other lessons learned. However, it is important to note that the purpose of these exploratory analyses is not to endorse any of these methods or to present specific recommendations for methodological changes to current standard assessment approaches.

A key goal of this effort was to compare specific alternative methods by applying them to economic models of different "SST scenarios." These scenarios were intended to reflect distinctly different types of SSTs, such as treatments for rapidly fatal conditions of childhood, treatments for non-fatal chronic diseases with substantial potential cost-offsets, etc. The goal of empiric testing was to determine the relative variation in the impact of different methods on different types of SSTs, and thereby to explore issues of face validity, ceiling or floor effects, and unintended consequences.

As noted in the text above, we did not feel that every potential alternative method warranted empirical testing. To guide this judgment, we considered the amount of support among methods experts and stakeholders, feasibility of implementation, experience of international HTA agencies, and our own sense of which methods had the greatest overall potential to address the four specific challenges of SSTs described at the outset of this paper.

5.2 SST Scenario Models

We applied alternative methods sequentially to three previously developed cost-effectiveness models developed in collaboration with ICER's academic modeling network. These models were selected to represent three very different types of condition-cost scenarios for SSTs.

SST for a fatal condition among children: Gene therapy for SMA Type 1

Details on the clinical aspects of Type 1 spinal muscular atrophy (SMA), current treatment options, and the body of evidence on clinical effectiveness are available in the original ICER report on this topic.[1] The economic model evaluated onasemnogene abeparvovec (Zolgensma®) compared to best supportive care (BSC). This model was developed before Zolgensma was launched and we therefore assumed a one-time price of $2 million. All subsequent adaptations for Zolgensma in this report were conducted using this price. Zolgensma is an SST for which a certain proportion of patients may be cured, and this is reflected in the base case approach that used cure proportion

techniques to model survival. This model was developed by academic collaborators at the School of Health and Related Research (ScHARR) at the University of Sheffield in the UK.[1]

The model was dependent on three constructs: the motor function milestones achieved, need for permanent ventilation, and the time to death. The motor function milestones included sitting and walking. Other interim motor function milestones such as head control, rolling, crawling, and standing were not modelled as explicit health states, but health benefits associated with such improvements were included as a utility benefit from the treatment. The model contained two main components: 1) a short-term model concordant with clinical study data, and 2) a long-term extrapolation model. Data inputs for the short-term model for each intervention were derived from their respective clinical trials and used directly to determine patient proportions in each health state at different time points in this model. The long-term model involved the extrapolation of motor function milestones, permanent ventilation status, and mortality rate, the latter of which was assumed to be conditional on health state, over a lifetime horizon using monthly cycles. In the base-case analysis, we assumed that the motor function milestones achieved at the end of follow-up in the clinical trials were sustained until death (i.e., patients stayed in the same motor function milestone-based health state until death).

SST for a chronic condition with high cost-offsets: A hypothetical treatment for Hemophilia A

This model was originally developed to compare the cost-effectiveness of emicizumab (Hemlibra®) prophylaxis to two alternative strategies (BPA prophylaxis and no prophylaxis) in patients with Hemophilia A with inhibitors to factor VIII who will not be treated with immune tolerance induction (ITI) or for whom ITI has been unsuccessful. This model was created by academic collaborators at the School of Pharmacy, University of Washington in Seattle.[3]

For the purposes of this exercise, we changed the nature of the intervention to model a hypothetical one-time treatment for these patients and focused on the population aged 12 years and over. The base case for the adapted model did not assume that the hypothetical treatment would cure any patients; rather, to ensure comparability with our original analysis, the hypothetical treatment was assumed to have the same effectiveness in reducing bleeds as Hemlibra, but with a single administration. We arbitrarily chose a $5 million price for this hypothetical SST. As will be described in a later section, we also created an optimistic scenario in which some patients would be cured by this treatment.

The Markov model included health states for individual bleed events as well as the development of joint arthropathy over time, with fewer joint bleeds over a lifetime leading to reduced levels of joint arthropathy. Patients entered the model based on the number of joints with arthropathy (0, 1, 2+) and from these sub-models transitioned from the “No Bleed” health state to “Untreated Bleeds”, “Treated Bleed Not into a Target Joint” or “Treated Target Joint Bleed” health states. Increases in the Pettersson score (a validated radiological scoring system that assesses the sum of joint damage in a patient) drove new arthropathy development (and transition between sub-models) and joint replacement surgery. The model was run with weekly cycle lengths.

SST for a fatal condition among adults: CAR-T for B-Cell lymphoma

This model evaluated axicabtagene ciloleucel (Yescarta®), a chimeric antigen receptor T-cell (CAR-T) therapy versus chemotherapy in adults with refractory aggressive B-cell lymphoma who are ineligible for autologous stem cell transplant. This model was developed by academic collaborators at the Skaggs School of Pharmacy, University of Colorado in Denver.[2]

A two-part partitioned survival model (a short-term decision tree and long-term semi-Markov model) was developed. Patient survival was calculated from available Kaplan-Meier survival curves from key trials which were digitized and extrapolated through five years after treatment initiation, at which point those alive and responding to treatment were considered effectively cured. After five years, those that were effectively cured exhibited mortality consistent with that of the general population. Those alive and not considered cured at the end of the five-year period transitioned to palliative chemotherapy. The model adopts a monthly cycle length.

SST Scenario Model Analyses

We applied alternative methods one at a time, retaining throughout the same time horizons and perspective (health care sector) as the originally published cost-effectiveness analyses. Because the aim of this evaluation exercise was to explore the impact of alternative methods on model outcomes compared to the prior base case results, we did not update the effectiveness or cost data used in the original analyses. For details on treatment efficacy, quality of life, and cost estimates, please refer to ICER's published reports on the therapies considered.[1-3]

The alternative methods that were tested are briefly described in the results section below. A model analysis plan with further details on the specific modeling scenarios is presented in Appendix D. For each of the three selected models, we present the results below by model for each research question and method tested. Costs and cost-effectiveness ratios are rounded to the nearest $1,000.

5.3 Empirical Analyses of Methods to Address Increased Uncertainty

5.3.1 Cure Proportion Modeling

Gene therapy for SMA Type 1

The base case analysis for the original assessment used cure proportion techniques to model survival. Testing other survival assumptions would have required extensive restructuring of this model, so we were not able to analyze switching to alternative methods for this SST scenario.

A hypothetical SST for Hemophilia A

We also could not perform a test of cure proportion modeling for the hypothetical treatment in the hemophilia model. The treatment had no mortality impact in our original model, and so we had no Kaplan-Meier data with which to fit survival curves.

CAR-T for B-Cell lymphoma

In assessing Yescarta for B-cell lymphoma, the original base case modeled a cure proportion using a flexible parametric survival curve where knots were introduced to allow the curve to plateau for patients who were alive and responding to treatment at 5 years, who were considered cured. Since we had used cure proportion modeling in the original analysis, to evaluate its impact for this exercise we developed a scenario using standard parametric survival analysis instead, without cure proportion or flexible parametric survival curve modeling. Parametric survival curve fitting is a standard approach when modeling survival in situations where cures are not expected. The differences between approaches is evident in the results presented in Table 5.1, where it is seen that not using a cure proportion and knots in the parametric curve markedly reduced overall costs and the calculated LYs and QALYs gained, producing higher incremental cost-effectiveness ratios as an overall effect.

Table 5.1. Cure Proportion Survival Analysis for Yescarta vs. Chemotherapy in Adult B-Cell Lymphoma

	Base Case (Flexible Parametric Curve Approach with Cure Proportion at 5 Years)		Scenario Using Standard Parametric Survival Analysis Without Cure Proportion or Flexible Parametric Curve	
	Yescarta	Chemotherapy	Yescarta	Chemotherapy
Costs	$617,000	$155,000	$545,000	$120,000
QALYs	5.87	2.48	2.19	0.55
LYs	7.35	3.23	3.17	0.94
Cost per QALY Gained	$112,000		$259,000	
Cost per LY Gained	$136,000		$190,000	

QALY: quality-adjusted life year; LY: life year

Summary

We were only able to compare cure proportion modeling versus traditional parametric survival analysis in the CAR-T model. In this example we found a substantial difference in the results, with large increases in estimated QALYs and LYs gained when the cure model is used and consequently a substantial reduction in estimated incremental cost-effectiveness ratios for the SST.

Cure proportion modeling is not time-intensive and even though we only tested it versus standard parametric survival analysis in one model, integration of cure proportion modeling into a wide variety of SST analyses appears feasible. The substantial variance in results in the CAR-T modeling exercise indicates the importance that assumptions around extrapolation of survival will have for SSTs. From a technical standpoint it appears advisable to model SSTs that show evidence of plateaus in survival data with newer techniques such as flexible parametric and other cure proportion analyses, using model fit statistics to determine the best fit to the available data. In such cases, traditional parametric curves may not adequately fit the available survival data due to the heterogeneity of the population (with some patients cured and others not). It should be noted that these survival analysis techniques still do not provide greater certainty regarding what we do not know (e.g., extrapolation of benefits for time points beyond which we have information). Overly optimistic cure proportion models could accentuate the risk that the payer is taking if there is a great deal of uncertainty and no long-term data, transferring that risk from the manufacturer to the payer. Where data are not mature enough to determine if the survival curve actually shows a sustained plateau, scenario analyses using various survival analytic techniques will help to characterize the range of potential results that may plausibly fit the available data to date.

In summary, the use of cure proportion models may help to better fit survival data in certain cases, and may be especially relevant for SSTs, where patients may be expected to have health outcomes that might be considered cures or at least long-term improvements. In such cases, analyses using this technique should produce estimates of costs and health gains that better reflect the available evidence compared to an analysis that does not employ cure proportion and/or flexible parametric survival modeling. Model fit statistics and visual inspection of modeled survival curves compared to Kaplan-Meier data from trials can be used to judge the fit of different survival analysis assumptions to the tail of the curve. However, without long-term survival data, it may be impossible to determine which survival curves are most accurate. In such cases, the presentation of results from several types of survival models can be used to develop a range around estimated long-term survival until more data become available.[2] Characterizing this uncertainty may help stakeholders as they consider mechanisms for transferring risk and costs if these potential survival benefits fail to be realized. For example, a rebate could be activated for a treatment if follow-up survival falls below the cure proportion assumed in the value-based price.

5.3.2 Model averaging

Model averaging would involve developing models with different structures and then averaging results across models. We chose not to pursue an empirical evaluation of this technique for two reasons. First, it is unclear if this would be practical for a typical HTA, as the development of several structurally differing models would be both time- and resource-intensive. Second, structural uncertainty is not relevant only to SSTs, but is considered an issue for cost-effectiveness analyses in general.

5.3.3 Conservative and Optimistic Scenario Analyses

As described earlier, we wished to evaluate the empiric results of developing a three-part scenario approach to inform decision-making: 1) the base case; 2) a plausible optimistic scenario; and 3) a plausible conservative scenario. All of the major changes in assumptions made to create these alternative scenarios for each of the three models are shown in Table 5.2.

As noted in the model analysis plan (Appendix D), the specific optimistic and conservative scenarios being tested here were not informed by systematic review or clinical expert opinion due to time constraints but were based on relatively arbitrary assumptions that were chosen for illustrative purposes. We chose to concentrate on variations in efficacy and cure rates as the variables likely to have a large impact and most relevant for SSTs. We acknowledge that more systematic exploration of parameter uncertainty through extensive sensitivity analyses would continue to be useful; these scenario analyses would be considered as complements to standard sensitivity analyses.

Table 5.2. Alternative Scenarios for Models

Model	Scenario	Description of Approach
SMA (Ellis, Stevenson, et al. 2019)[1]	Base case	The model was dependent on three primary outcomes: the motor function milestones achieved, need for permanent ventilation, and the time to death. The key motor function milestones were sitting and walking.
	Optimistic	We assumed a cure proportion for patients treated that represented a 25% increase in the percentage of patients being able to walk as compared to the base case analysis.
	Conservative	We assumed a 50% drop in cure proportion of those patients being able to walk 10 years after patients entered the model; these patients instead were assumed to have achieved only a sitting health state.
Hemophilia (Rind, Guzauskas, et al. 2018)[2]	Base case	This model was structured to track various bleed events, the development of arthropathy due to bleeds, and quality-adjusted life expectancy over time. The hypothetical SST scenario was framed with the new SST having the same effectiveness as Hemlibra but delivered as a single treatment at a cost of $5 million.
	Optimistic	We assumed that 50% of treated patients were cured and had no further bleeds, with the attendant benefits of higher QALYs and lower costs.
	Conservative	We assumed that patients treated with the hypothetical SST had a 25% increase in bleed events compared to the base case (Hemlibra) bleed rates. Because Hemlibra did not have any effect on patient survival in the original model and we assumed the same in this model adaptation, there are no changes in LYs gained or the incremental results associated with this metric.
CAR-T (Tice, Whittington, et al. 2018)[3]	Base case	The model was a partitioned survival model from assessment of response to five years after treatment completion, followed by a Markov model from five years until death. Patients who were alive and responding to treatment at 5 years were assumed to be long-term survivors and considered to be effectively cured.
	Optimistic	We assumed that those alive at the end of the first two years of the model were considered cured, using a cure-proportion modeling approach, in addition to introducing flexible parametric survival curve modeling.
	Conservative	We assumed no cure proportion, and used the standard parametric model fit, with no knots in the survival curves to account for flattening seen in the original survival curves.

Gene therapy for SMA Type 1

The optimistic scenario for Zolgensma assumed an arbitrary 25% increase in the percentage of patients being able to walk as compared to the base case analysis, with this improvement contributed by upgrading the outcomes of 25% of patients who only achieved a sitting health state. This translated to the proportion of patients able to walk increasing from 16.7% in the base case to 20.8% in this scenario. The proportion of those not able even to sit remained at 20.8%. For the conservative scenario, we assumed an arbitrary 50% drop in cure proportion 10 years after patients entered the model. This led to a decrease in the proportion walking, from 16.7% to 8.3%, and an increase in the proportion sitting, from 59% to 67%, at the ten-year time point in the model. Total costs, QALY and LY gains, as well as incremental cost-effectiveness results of the optimistic and conservative scenarios are presented along with the base case results in Table 5.3.

Table 5.3. Optimistic & Conservative Scenario Analyses for Zolgensma vs. BSC in SMA Type 1

	Base Case		Optimistic Scenario		Conservative Scenario	
	Zolgensma	BSC	Zolgensma	BSC	Zolgensma	BSC
Costs	$3,657,000	$789,000	$3,638,000	$789,000	$3,673,000	$789,000
QALYs	12.23	0.46	12.83	0.46	11.23	0.46
LYs	18.17	2.4	18.64	2.4	17.3	2.4
Cost per QALY Gained	$243,000		$230,000		$268,000	
Value-Based Price at $150,000/QALY	$899,000		$1,000,000		$733,000	

Optimistic Scenario Results

Compared to the base case results, we found that total costs for Zolgensma decreased only by approximately 1%, while total QALYs and LYs increased by approximately 5% and 3%, respectively. The incremental cost per QALY ratio only decreased by approximately $13,000, but because this SST is administered as a one-time therapy, even a small difference in the cost/QALY ratio can translate into relatively large absolute differences in the value-based price – in this case a difference of $100,000 at a threshold of $150,000/QALY. Costs seen in this scenario do not vary greatly from the base case analysis because a large majority of total treatment costs are contributed by the one-time upfront cost of the gene therapy and these costs are incurred by patients in either scenario. In addition, although there are a greater proportion of patients in the "walking" health state, which has lower costs than the "sitting" health state, these patients still incur higher health care costs compared to the general population. In this case, in which the optimistic scenario is based on assumptions that are not major cost or QALY drivers, it is striking to note the relatively large absolute impact on the value-based price for this SST.

Conservative Scenario Results

There was no substantial change in total costs for Zolgensma and an approximate 8% and 5% decrease in QALYs and LYs respectively compared to the base case results. The incremental cost effectiveness ratio increased by nominal amounts: approximately $24,000 per QALY gained. As with the optimistic scenario, this relatively small change in the cost/QALY translated into a large absolute difference in the associated value-based price given that this price concentrates what would have been small changes in price over patients' lifetimes into a large change in a single-administration price.

A hypothetical SST for Hemophilia A

As described above, for the optimistic scenario with a hypothetical SST for hemophilia A, we arbitrarily assumed that 50% of patients were cured upon treatment and had no subsequent bleeding episodes for the rest of their lives. Those patients considered cured were assumed to accrue treatment costs and QALYs as for a hemophilia population with no bleeds. We assumed that the remaining 50% of patients accrued non-SST health care costs and QALYs equal to those of the population treated with Hemlibra in the original model. For the conservative scenario, we assumed that all patients had a bleed rate worse than with Hemlibra, by assuming a 25% increase in bleed events compared to those observed with Hemlibra in the base case analysis. Though the hypothetical SST produced a cure for 50% of patients, it does not increase length of life, so there were no changes in LYs gained. The only impact of the cure fraction was an increase in the quality of life (and decrease in bleed-related costs) due to the reduction in bleeds.

Total costs, QALY and LY gains, as well as incremental cost-effectiveness results of the base case, optimistic, and conservative scenarios are presented below in Table 5.4. It should be noted here that while the base case effectiveness assumed for this SST reflects that seen for Hemlibra in ICER's published Hemophilia A report, the cost differs since we are assuming a $5 million one-time cost for this hypothetical SST. Although the hypothetical SST was found to be cost saving, we calculated value-based prices under each scenario for illustrative purposes, demonstrating the very high prices that can result when cost offsets are completely captured in the value-based price.

Table 5.4. Optimistic & Conservative Scenario Analyses for Hypothetical SST with $5 Million Price vs. BPA Prophylaxis in Hemophilia A Patients with Inhibitors

	Base Case			Optimistic Scenario			Conservative Scenario		
	Hypothetical SST	BPA Prophylaxis	Increment	Hypothetical SST	BPA Prophylaxis	Increment	Hypothetical SST	BPA Prophylaxis	Increment
Costs	$9,269,000	$90,182,000	($80,913,000)	$7,165,000	$90,182,000	($83,017,000)	$10,285,000	$90,182,000	($78,515,000)
QALYs	15.41	15.21	0.2	15.74	15.21	0.53	15.34	15.21	0.11
LYs	21.28	21.28	0	21.28	21.28	0	21.28	21.28	0
Cost per QALY Gained	Cost-saving*			Cost-saving*			Cost-saving*		
Value-Based Price at $150,000/QALY	$86,000,000			$88,000,000			$85,000,000		

Optimistic Scenario

Compared to the base case results, total intervention costs decreased by approximately 23% ($7,165,000 versus $9,269,000) while the QALY increase was approximately 2% (15.74 versus 15.41). In this optimistic scenario, lower costs are driven by the absence of bleed-related costs among the 50% of treated patients who are cured, while the higher QALYs reflect the better quality of life in patients with no bleeds. As in the base case, this scenario also produces incremental cost per QALY results that show this hypothetical treatment to be cost saving. The value-based price in this scenario increased marginally to $88,000,000 compared to the base case threshold price of $86,000,000. While costs decrease in this scenario due to fewer bleeds, there is only a small impact on QALYs gained because of the lack of mortality benefit and the intermittent impact of bleeds on quality of life. This, combined with the relatively higher cost of the BPA prophylaxis arm compared to the hypothetical SST arm, leads to a relatively small change in the value-based price in this scenario. The magnitude of these prices generated by applying traditional cost-effectiveness thresholds will be addressed more directly in the section below testing different approaches to "shared savings."

Conservative Scenario

With poorer outcomes (bleed rates higher than in the Hemlibra base case) and no patients assumed to be "cured" (i.e., 0% cure proportion), this scenario results in total intervention costs approximately 11% higher and QALYs marginally (<1%) lower than those in the base case. Higher total costs are driven by higher costs to treat bleeds, while lower QALYs are due to a higher bleed rate compared to what was observed in the base case analysis. However, due to the substantially higher costs of the comparator BPA prophylaxis arm, this scenario also resulted in incremental cost per QALY results that show this hypothetical treatment to be cost saving. The value-based price decreased relatively little (albeit $1 million dollars) from $86,000,000 in the base case to $85,000,000 under this scenario. As above, there is only a small impact on QALYs gained, and a very high cost for the BPA prophylaxis arm compared to the hypothetical SST arm, which leads to a relatively small proportional change in the value-based price in this scenario.

CAR-T for B-Cell Lymphoma

In the optimistic scenario, we assumed that those alive at the end of the first two years of the model were considered cured – as opposed to the base case assumption that patients were only cured if they were free of disease at five years after treatment. For the conservative scenario, we assumed no cure proportion, and used the standard parametric model fit, with no knots in the survival curves to account for flattening seen in the original survival curves. Total costs, QALY and LY gains, as well as incremental cost-effectiveness results of the optimistic and conservative scenarios are presented along with the base case results in Table 5.5.

Table 5.5. Optimistic & Conservative Scenario Analyses for Yescarta vs. Chemotherapy in Adult B-Cell Lymphoma

	Base Case		Optimistic Scenario		Conservative Scenario	
	Yescarta	Chemotherapy	Yescarta	Chemotherapy	Yescarta	Chemotherapy
Costs	$617,000	$155,000	$649,000	$157,000	$545,000	$120,000
QALYs	5.87	2.48	7.62	2.72	2.19	0.55
LYs	7.35	3.23	9.19	3.37	3.17	0.94
Cost per QALY Gained	$136,000		$100,000		$259,000	
Value-Based Price at $150,000/QALY	$424,000		$635,000		$180,000	

QALY: quality-adjusted life year; LY: life year

Optimistic Scenario

Compared to the base case, we noted an approximate 30% increase in QALYs, 5% increase in total costs, and almost two additional years of life gained with Yescarta treatment. The higher costs are attributed to health care costs in a higher proportion of patients alive, with QALYs and LYs gained reflecting the greater proportion of patients being cured. Incremental cost-effectiveness ratios decreased by approximately $36,000 per QALY gained. While the value-based price at $150,000 per QALY increased from $424,000 in the base case to $635,000. In this scenario, QALYs increased in both the treatment and comparator arms (albeit by more in the treatment arm), leading to a modest change in incremental QALYs. Combined with the small increase in incremental costs, this led to a relatively modest decrease in the incremental cost-effectiveness ratio. As was also seen in the case of Zolgensma, however, with one-time therapies the effect of small changes in cost/QALY findings will translate into large relative and absolute differences in value-based prices, highlighting again how sensitive the results of evaluations of one-time treatments can be to uncertainty.

Conservative Scenario

Compared to the base case, we noted an approximate 63% decrease in QALYs, more than 50% decrease in LYs gained, and a 12% decrease in total costs. The lower costs and poorer outcomes were due to use of the parametric curve fitting without adjusting for flattening of the curve using a flexible parametric approach, resulting in poorer estimated survival in the modeled cohort. Incremental cost effectiveness ratios increased by approximately $123,000 per QALY gained, while

the value-based price decreased from $424,000 in the base case to only $180,000 in this scenario. The noticeable increase in the incremental costs per QALY gained in this conservative scenario is driven largely by the major drop in QALYs and incremental QALYs gained in this scenario where no patients are considered "cured" at any point in time. The assumption of no cures leads to larger impacts in this scenario than in the prior optimistic scenario, which simply varied when a "cure" was assumed to occur.

Summary

The results of our alternative scenarios for the SMA model showed small changes in total costs, with moderate changes in QALY and LY gains, compared to the base case results. This resulted in relatively modest changes to the incremental cost-effectiveness ratios for these scenarios when compared to the base case, but a large impact on value-based prices, which ranged from $733,000 to $1,000,000. The alternative scenarios we tested in the hemophilia A model led to relatively large changes in total costs but only minor changes in QALYs gained when compared to the base case. However, in all scenarios the hypothetical treatments remained cost-saving relative to the comparator, due to the very high cost of BPA prophylaxis in these hemophilia patients with inhibitors, and there were only modest impacts on the value-based prices. The results for the alternative scenarios in the B-cell lymphoma model showed more noticeable differences in costs and outcomes, with greater differences in magnitude for outcomes. This resulted in more consequential changes to the incremental cost-effectiveness ratios and to the magnitude of value-based prices.

These results point out that if alternative scenarios are based on assumptions that are not major cost or QALY drivers, they are not likely to have much impact on decisions. As stated above, the optimistic and conservative scenarios tested here were not informed by clinical expert opinion but were based on assumptions chosen for illustrative purposes only. In actual practice, the inputs and assumptions for these alternative scenarios would be developed with input from clinical experts, manufacturers, and patients, by eliciting details of optimistic and conservative scenarios that they believe could plausibly occur with these new treatments. While uncertainty around long-term benefits would remain, the cost-effectiveness model could be used to assess what value for key effectiveness parameters would be needed to produce the outcomes under each scenario. In addition, probabilistic sensitivity analyses could be used to give some sense of the likelihood of such scenarios, given base case assumptions.

This exercise represents a very small pilot test of how results could vary across base case, optimistic, and conservative scenarios developed for the evaluation of SSTs. The fact that we found variation in results related to value-based pricing that differed relatively little in some cases (hemophilia A), and more in others (SMA and CAR-T) suggests that such an approach could provide one way to make more transparent the relative uncertainty in results for SSTs, but what remains unknown is the impact on decision-makers. It is possible that having three explicit scenarios would

address a vague sense of concern among some who worry about the results of a model that must make very consequential assumptions about key model parameters, such as the cure proportion or the durability of treatment effect. When the results of conservative and optimistic scenarios differ little from the base case, it may allow decision-makers to move forward with less unexplored variation in their individual views of the impact of uncertainty on their overall judgment of treatment value.

However, there are potential unintended consequences of focusing decision-makers on these three prominent scenarios. Decision-makers might rely on these "validated" scenarios to the exclusion of more varied consideration of univariate and probabilistic sensitivity analyses, as well as other relevant scenario analyses. On the other hand, where a "best estimate" scenario cannot be defined by decision-makers, it is challenging to deal with a wide range of possible scenarios. In addition, different HTA groups will view the relative benefits and disadvantages of using a three-scenario approach differently depending on their current methods for deliberation with independent appraisal committees. CADTH currently does this as part of the standard set of sensitivity analyses and consider it to be good practice. As noted earlier, for some HTA groups, such as NICE, manufacturers provide a model for consideration, an academic group provides an alternative, and the appraisal committee is presented both versions to consider during deliberation, along with a range of scenario analyses. For HTA groups such as ICER that do not begin with manufacturer models, although developing three formal scenarios may help push the process toward inclusion of a broader set of potentially plausible results, there may be important unintended consequences that merit caution.

5.3.4 Probabilistic sensitivity analysis and linkage to a secondary "uncertainty" criterion

As stated above, the JCVI in the United Kingdom has proposed that positive funding decisions for vaccines should only be taken when at least 95% of scenarios in a Monte Carlo simulation are below the standard £30,000 threshold.[47] We tested a similar potential constraint, calculating the value-based price at which 90% of simulations fell below the $150,000 per QALY threshold and contrasting this with the deterministic base case price at the $150,000 per QALY threshold.

SMA Type 1

Based on multiple simulation runs, we calculated the price to reach the $150,000 per QALY threshold with at least 90% of simulation runs producing incremental cost per QALY results at or below this threshold. Using this constraint would result in a value-based price of $790,000 for Zolgensma in type 1 SMA, as compared to $899,000 in the base case, a reduction of over $100,000 that, because of the scale of the price, represents only a 12% decrease. This value-based price lies in between the result of the conservative scenario described above ($733,000) and the base case result.

Table 5.6. Value-Based Price Criteria for Zolgensma in SMA Type 1

	Deterministic Base Case	Price at 90% ≤$150,000/QALY
$150,000 per QALY	$899,000	$790,000

QALY: quality-adjusted life year

Hemophilia A

All existing and hypothetical treatments for Hemophilia A were found to be cost-saving in our base case analysis, with 100% of simulations being cost-saving in the probabilistic analyses as well in this situation in which the health care system is already paying substantially for BPA prophylaxis. Despite this, we derived value-based prices at the $150,000 per QALY willingness-to-pay threshold for the base case, and using the 90% criterion. Because of the high cost offset from avoidance of BPA prophylaxis for these patients, the base case analysis resulted in a value-based price of $85,942,000 for the hypothetical SST. In contrast, requiring 90% of probabilistic simulations to be at or below $150,000 per QALY resulted in a value-based price of $72,800,000, a 15% decrease. This price is also lower than the $85M price suggested in the conservative scenario above.

Table 5.7. Value-Based Price Criteria for Hypothetical SST in Hemophilia Patients with Inhibitors

	Deterministic Base Case	Price at 90% ≤$150,000/QALY
$150,000 per QALY	$85,942,000	$72,800,000

QALY: quality-adjusted life year

B-Cell Lymphoma

Simulations were also run in the B-cell lymphoma model to calculate the price to reach the $150,000 per QALY threshold with at least 90% of simulation runs producing incremental cost per QALY results at or below this threshold. This resulted in value-based price of approximately $315,000, as compared to the base case price of $424,000 at the $150,000 per QALY threshold, a 26% decrease. This price is much higher than the value-based price ($180,000) found in the conservative scenario above.

Table 5.8. Value-Based Price Criteria for Yescarta (without Hospital Mark-Up) vs. Chemotherapy in Adult B-Cell Lymphoma

	Deterministic Base Case	Price at 90% ≤$150,000/QALY
$150,000 per QALY	$424,000	$315,000

QALY: quality-adjusted life year

Summary

The use of different probability filters at specific willingness-to-pay thresholds to constrain the value-based price range seemed feasible to put into practice. As expected, the requirement that 90% of simulated cost-effectiveness ratios fall below $150,000 per QALY led to lower value-based prices than found in the deterministic base cases (by 12% to 15%). This reflects the requirement for increased certainty that the intervention is actually cost-effective at a given level, effectively decreasing the willingness-to-pay threshold.

This procedure would be a valid method to provide a higher level of certainty that prices are more likely to be cost-effective at the upper end of the range. However, there are potential limitations of this method that should be considered. First, it is unclear how the specific percentage threshold should be selected, whether it is 95% as suggested by the JCVI or 90% as modeled here; both are arbitrary. Second, this technique relies on the use of probabilistic sensitivity analyses with multiple simulations. Performing these analyses may be time- and resource-intensive, especially for more complex models or those with shorter cycle lengths. In addition, the results of these analyses are sensitive to the ranges and distributions of values used in the sensitivity analyses. In the cases of immature data for SSTs, there may be asymmetry in that the longer-term data could only be worse than in the short term. Thus, it is possible that the most plausible ranges could overestimate effectiveness based on early data. In applying this more stringent approach, there is therefore still the danger of not adequately managing payer risk for products that appear to be very beneficial to patients but where the magnitude and variance of that benefit is not known. Finally, values for some variables may be correlated with those for other variables, and that correlation should be considered when sampling for probabilistic simulations. However, that information may be unavailable or difficult to obtain.

As noted above, it may be of interest for decision-makers to compare the results of this approach to those of the "conservative" scenario described earlier. Both methods address uncertainty but do so in very different ways. It is possible that decision-makers may find them complementary and therefore helpful in exploring ways to understand and apply relative uncertainty to judgments of value and recommendations for value-based prices. Cost effectiveness acceptability curves are another approach to address the opportunity costs of SSTs and signal the uncertainty to decisionmakers. Whether viewed as an advantage or disadvantage, the application of a PSA uncertainty criterion could also be implemented as an explicit method consistently across different types of SSTs to arrive at a single determination. While some might view that as a helpful approach that maximizes consistency and transparency, its use as a decision rule would lead to inefficiencies, in that some SSTs that could be considered cost-effective would no longer be accepted under this more stringent threshold. Other groups might view this as too algorithmic to use as a process for transferring risk, and as detracting from the richness of a broader view of uncertainty and its application to judgments within a deliberative process. For example, some might argue that greater

uncertainty might be acceptable when dealing with potentially curative treatments for life threatening conditions.

5.3.5 Probabilistic sensitivity analysis and a secondary policy requirement for outcomes-based payment

No empirical analysis of this method is relevant for its consideration as an alternative method for the evaluation of SSTs.

5.4 Time Divergence Between Costs and Benefits

5.4.1 Applying Different Uniform and Differential Discount Rates

Based on our review of the literature and interviews with methods experts and stakeholders we selected three discounting scenarios for empirical testing, as shown below in Table 5.9. A discounting rate of 3% was selected as one anchor as it represents the current recommendation from the Second Panel on Cost-Effectiveness in Health and Medicine in the US.[23] Similarly, the other major discounting rate evaluated was 1.5%, which represents the level selected for use by CADTH for all analyses, and is also the level that can be considered under special circumstances by NICE.

Table 5.9. Discounting Scenarios

	Discount Rate for Costs	Discount Rate for Outcomes
Base Case	3%	3%
Lower Discount Rates	1.5%	1.5%
Differential Discounting	3%	1.5%

SMA Type 1

Results using different uniform and differential discounting rates are shown below in Table 5.10. A lower (1.5%) discount rate for costs and outcomes increases the total cost by a magnitude of 9% and 6% for Zolgensma and basic supportive care (BSC), respectively, a relatively small net difference of 3%. But the impact on health outcomes is substantial. QALYs for Zolgensma increase by 30% from 12.23 to 16.29, whereas the QALYs for BSC increase by a more modest 6%. The magnitude of the cost increase for Zolgensma is lower than that for QALYs because the cost of Zolgensma is incurred at time 0 where there is no effect of discounting in the model. Using a 1.5% discount rate for both costs and outcomes drives a reduction in overall incremental cost-effectiveness ratio from $243,000/QALY (at 3% discount rate) to $199,000/QALY.

Applying a differential discounting approach, where only the health outcome discount rates are lowered to 1.5%, we see the same 30% increase in QALYs compared to 3% discounting, and the cost/QALY produced ($188,000/QALY) is similar to that when a uniform 1.5% discount rate is used for both outcomes and costs.

As another way to evaluate the impact of the alternative discounting methods, the value-based prices (at $150,000 per QALY) calculated under these scenarios increased from $899,000 at uniform 3% discounting, to $1,200,000 using a 1.5% uniform discount rate, to approximately $1,500,000 with differential discounting of costs at 3% and outcomes at 1.5%. The magnitude of the variation across these results suggests that alternative discounting methods are among the most

consequential options to be considered for the evaluation of interventions that are estimated to produce long-term clinical benefits comparable to Zolgensma with a single or short-term treatment.

Table 5.10. Discounting Scenarios for Zolgensma vs. BSC in SMA Type 1 Assuming a $2 Million Price for Zolgensma

	Base Case Uniform Discounting Costs: 3% Outcomes: 3%		Lower Uniform Discounting Costs: 1.5% Outcomes: 1.5%		Differential Discounting Costs: 3% Outcomes: 1.5%	
	Zolgensma	BSC	Zolgensma	BSC	Zolgensma	BSC
Costs	$3,657,000	$789,000	$3,976,000	$834,000	$3,657,000	$789,000
QALYs	12.23	0.46	16.29	0.48	16.29	0.48
LYs	18.17	2.4	23.62	2.53	23.62	2.53
Cost per QALY Gained	$243,000		$199,000		$181,000	
Value-Based Price at $150,000/QALY	$899,000		$1,200,000		$1,500,000	

QALY: quality-adjust life year; LY: life year; BSC: best supportive care

Hemophilia A

We report the results for the hypothetical hemophilia SST across the different discounting scenarios in Table 5.11. The nature and magnitude of the differences across various discounting approaches are similar to that described for Zolgensma above. As seen with Zolgensma, lower uniform discounting shows a higher relative gain in QALYs compared to increases in cost, thereby driving down the incremental cost-effectiveness ratio. Differential discounting, with costs still discounted at 3% but outcomes discounted only at 1.5% produces superior cost-effectiveness for an SST.

The value-based prices calculated under these scenarios increased from $85,942,000 in the base case to approximately $109,000,000 using a lower discount rate. Interestingly, the value-based price using differential discounting (1.5% for outcomes and 3% for costs) differed only slightly from the base case value-based price. While differential discounting produces more QALYs in each treatment arm than with uniform discounting at 3%, the incremental gain in QALYs is similar, increasing from 0.20 QALYs gained to 0.25. Because the difference in outcomes (QALYs gained) was very small in this case while costs were unchanged from the base case and are very large relative to the incremental QALYs gained, the change in discount rate for outcomes had a relatively minor impact on the value-based price in this case.

Table 5.11. Discounting Scenarios for Hypothetical SST at $5 Million Price vs. BPA Prophylaxis in Hemophilia A Patients with Inhibitor

	Base Case : Uniform Discounting Costs: 3% Outcomes: 3%			Lower Uniform Discounting Costs: 1.5% Outcomes: 1.5%			Differential Discounting Costs: 3% Outcomes: 1.5%		
	One-Time SST	BPA Prophy.	Increment	One-Time SST	BPA Prophy.	Increment	One-Time SST	BPA Prophy.	Increment
Costs	$9,269,000	$90,182,000	$80,913,000	$10,447,000	$114,887,000	$104,440,000	$9,269,000	$90,182,000	$80,913,000
QALYs	15.41	15.21	0.2	19.66	19.41	0.25	19.66	19.41	0.25
LYs	21.28	21.28	0	27.2	27.2	0	27.2	27.2	0
Cost per QALY Gained	Cost-saving*			Cost-saving*			Cost-saving*		
Value-Based Price at $150,000/ QALY	$85,942,000			$109,477,000			$85,950,000		

QALY: quality-adjusted life year; LY: life year; SST: single or short-term treatment; BPA Prophy: by-passing agent prophylaxis
*Dominant strategy

B-Cell Lymphoma

Results for the B-cell lymphoma model using the base case discounting rates, lower uniform discount rates, and differential discounting are reported in Table 5.12.

The results show the same trends seen in the other models but at much lower magnitude of difference given that the QALY gains in the base case are more modest (5.87). The different discounting approaches produce a range of total QALYs from 5.87 in the base case with 3% uniform discounting up to a high of 6.99 with 1.5% discounting results. The value-based prices calculated under these scenarios increased from $424,000 at uniform 3% discounting, to $517,000 using a 1.5% uniform discount rate, to approximately $536,000 with differential discounting of costs at 3% and outcomes at 1.5%.

Yescarta does not provide a true cure for most treated patients, and is also a treatment of adults, and therefore the magnitude of the change in QALYs produced is far smaller than that seen for Zolgensma or the hypothetical Hemophilia A SST. This demonstrates that applying different discounting methods will have a far larger impact on SSTs for children or young adults than older populations. HTA groups and decision makers should consider whether this effect may represent an intended effect or whether it raises concerns about (over) favoring treatments for the young at the expense of the elderly.

Table 5.12. Discounting Scenarios for Yescarta vs. Chemotherapy in Adult B-Cell Lymphoma

	Base Case Analysis Costs: 3% Outcomes: 3%		Variable Discounting Costs: 1.5% Outcomes: 1.5%		Differential Discounting Costs: 3% Outcomes: 1.5%	
	Yescarta	Chemotherapy	Yescarta	Chemotherapy	Yescarta	Chemotherapy
Costs	$617,000	$155,000	$645,000	$166,000	$617,000	$155,000
QALYs	5.87	2.48	6.99	2.91	6.99	2.91
LYs	7.35	3.23	8.7	3.75	8.7	3.75
Cost per QALY Gained	$136,000		$117,000		$113,000	
Value-Based Price at $150,000/QALY	$424,000		$517,000		$536,000	

QALY: quality-adjusted life year; LY: life year

Summary

Analyses considering various discount rates were simple to implement in these cost-effectiveness models. The results of our analyses changed in the expected direction but continue to present normative questions regarding the theoretical justification for discounting in economic evaluation. Not surprisingly, the use of a lower discount rate (1.5% in this case) than in the base case (at 3%) led to more favorable results in each of these cases. For SSTs that have a one-time up-front cost, changes in the discount rate have a larger impact on outcomes (which are streamed over time) than on costs (which are concentrated in the present). Lowering the discount rate therefore makes these types of interventions look relatively more cost-effective, as also shown in a recent report on methods for evaluating regenerative medicines in the UK.[11] However, there is no conceptual basis for changing the rate of time preference depending on the technology being evaluated, so more empirical work would be needed to support this change should it be contemplated only for SSTs.

With differential discounting (lowering the health outcome discount rate to 1.5% while leaving the cost rate at 3%), health outcomes over time will decline in present value more slowly than costs over the same time period. This leads to a relative increase in health outcomes but not costs compared to the base case (and therefore to better incremental cost-effectiveness ratios), regardless of when costs are incurred. However, it will have a larger relative impact on incremental cost-effectiveness ratios in cases where most of the intervention costs occur in the present, as may be the case with SSTs.

As noted above, the empirical results shown in this section cannot answer the conceptual, normative questions about discounting, they can only demonstrate the magnitude of their effect in a small number of test cases. What is clear is that minor differences in discount rate will have significant effects on the estimated cost-effectiveness of SSTs, and therefore it is imperative that policymakers should focus considerable attention on this methodological element in considering whether to adopt new methods specifically for SSTs as opposed to other treatments. Health economists often address normative differences by presenting multiple different scenario analyses and letting decision-makers wrestle with how to reconcile various perspectives. In the case of discounting it is unknown how HTA appraisal committees or ultimate decision-makers will react to presentation of multiple results based on different discounting approaches. Without training in the background issues, providing multiple sets of results may result in confusion, lack of consistency from one appraisal committee to another, and other unintended consequences. Further study of methods to justify discounting rates and whether to present decision-making bodies with multiple scenarios is highly needed.

5.5 Affordability and Fair Sharing of Economic Surplus

5.5.1 Shared Savings

As described earlier, we sought to empirically test cost-effectiveness analyses in which different proportions of the cost offset that is estimated to be generated by an SST is "shared" by the innovator and by the health system/society. To perform these evaluations, we developed analyses using two different approaches to shared savings: 1) one in the which 50% and 100% of the cost offsets were shared (retained) by the health system, rather than having all cost offsets included in the price accorded to the innovator in the base case; and 2) one in which 100% of costs in the comparator arm are retained for inclusion in a value-based price for the SST up to 12 years in the model, following which these cost offsets are set to zero. This latter approach we labeled the "length of exclusivity" approach (LOE).

SMA Type 1

The results of these analyses for Zolgensma in SMA Type 1 are shown in Table 5.13 below. The value-based price decreases from $899,000 in the base case to $504,000 with 50% sharing of the cost offsets between innovator and health system, and drops to $109,000 when the innovator payment represents full price for the QALYs gained but the innovator receives 0% of the cost offsets from treatment. The LOE scenario (with no cost offset after 12 years) did not create a substantial difference in the value-based price compared to the base case analysis, decreasing from $899,000 to $860,000. This is largely because there are few cost offsets beyond 12 years in the base case due to the high mortality rate of patients in the best supportive care (comparator) arm of the model.

Tabxle 5.13. Value-Based Price Based on Cost-Offsets Captured for Zolgensma in SMA Type 1

Zolgensma vs. BSC		Costs	QALYs	LY	Cost per QALY Gained	Value-Based Price at $150,000/QALY
Base Case (No Shared Savings)	Zolgensma	$3,657,000	12.23	18.17	$243,000	$899,000
	BSC	$789,000	0.46	2.4		
	Incremental	$2,868,000	11.77	15.77		
50% Shared Savings	Zolgensma	$3,657,000	12.23	18.17	$277,000	$504,000
	BSC	$395,000	0.46	2.4		
	Incremental	$3,262,000	11.77	15.77		
100% Shared Savings	Zolgensma	$3,657,000	12.23	18.17	$311,000	$109,000
	BSC	$0	0.46	2.4		
	Incremental	$3,657,000	11.77	15.77		
LOE Scenario Shared Savings	Zolgensma	$3,657,000	12.23	18.17	$247,000	$860,000
	BSC	$750,000	0.46	2.4		
	Incremental	$2,907,000	11.77	15.77		

BSC: best supportive care, LOE: loss of exclusivity, QALY: quality-adjusted life year

Hemophilia A

Best supportive care for Hemophilia A when patients have inhibitors is extremely expensive, and therefore any shared savings method is likely to have a very large impact on incremental cost-effectiveness and related value-based price recommendations. At 50% shared savings, the value-based price drops from $86 million to approximately $41 million. We were unable to estimate a positive price for the hypothetical SST in the 100% shared savings scenario, because additional non-therapy costs were substantial enough that a negative cost would need to be attributed to the intervention to reach the $150,000 per QALY threshold. Therefore, the calculation of value-based price was not relevant for a scenario in which all cost offsets were retained by the health system. The value-based price in the LOE scenario decreased to $38.1 million, even further than the 50% shared savings method, reflecting the large impact in this case of reducing cost offsets beyond year 12 in the model due to the relatively long life span of these patients.

Table 5.14. Value-Based Price Based on Cost-Offsets Captured for Hypothetical SST in Hemophilia A

Hypothetical SST vs. BPA Prophylaxis		Costs	QALYs	LYs	Cost per QALY Gained	Value-Based Price at $150,000/QALY
Base Case (No Shared Savings)	Hypothetical SST	$9,269,000	15.41	21.28	Cost-saving	$86,000,000
	BPA Prophylaxis	$90,182,000	15.21	21.28		
	Incremental	($80,913,000)	0.2	-		
50% Shared Savings	Hypothetical SST	$9,269,000	15.41	21.28	Cost-saving	$40,851,000
	BPA Prophylaxis	$45,091,000	15.21	21.28		
	Incremental	($35,822,000)	0.2	-		
100% Shared Savings	Hypothetical SST	$9,269,000	15.41	21.28	$47,482,000	No positive price could be calculated due to high non-therapy costs
	BPA Prophylaxis	$0	15.21	21.28		
	Incremental	$9,269,000	0.2	-		
LOE Scenario Shared Savings	Hypothetical SST	$9,269,000	15.41	21.28	Cost-saving	$38,068,000
	BPA Prophylaxis	$42,309,000	15.21	21.28		
	Incremental	$2,907,000	0.2	-		

LOE: loss of exclusivity, QALY: quality-adjusted life year

B-Cell Lymphoma

We also re-calculated incremental cost-effectiveness and associated value-based price benchmarks for Yescarta versus chemotherapy assuming 50% and 100% shared savings. When these levels of shared savings were used to derive value-based prices at the $150,000 per QALY threshold, the value-based price decreased from $424,000 in the base case to $340,000 at 50% and $257,000 with 100% of savings shared back with the health system. Using the LOE scenario, the change in value-based price was more modest, decreasing only to $399,000. As expected, this was not very different from the base-case price, given that most of the costs for this disease state are incurred up-front.

Table 5.15. Value-Based Price Based on Cost-Offsets Captured for Yescarta in Adult B-Cell Lymphoma

Yescarta vs. Chemotherapy		Costs	QALYs	LYs	Cost per QALY Gained	Value-Based Price at $150,000/QALY*
Base Case (No Shared Savings)	Yescarta	$617,000	5.87	7.35	$136,000	$424,000
	Chemotherapy	$155,000	2.48	3.23		
	Incremental	$462,000	3.4	4.12		
50% Shared Savings	Yescarta	$617,000	5.87	7.35	$159,000	$340,000
	Chemotherapy	$77,000	2.48	3.23		
	Incremental	$539,000	3.4	4.12		
100% Shared Savings	Yescarta	$617,000	5.87	7.35	$182,000	$257,000
	Chemotherapy	$0	2.48	3.23		
	Incremental	$617,000	3.4	4.12		
LOE Scenario Shared Savings	Yescarta	$617,000	5.87	7.35	$143,000	$399,000
	Chemotherapy	$131,000	2.48	3.23		
	Incremental	$486,000	3.4	4.12		

LOE: loss of exclusivity, QALY: quality-adjusted life year

*Does not include hospital markup.

Summary

As expected, assigning cost offsets so that 50% or 100% are "shared" with the health system through the calculation of a lower value-based price had the largest impact when applied to SSTs for chronic conditions with very expensive supportive care. In such cases, SSTs have the potential to lead to very large cost offsets that, along with significant QALY gains, translate into extremely high value-based prices. The presentation and discussion of shared savings scenarios could provide useful information that would foster an open dialogue about the degree to which economic surplus should be shared between innovators and the health system in a context of federal investment in research and the likelihood that many SSTs will never face true generic/biosimilar competition. Note that for short-term, fatal conditions, this approach will have less of an impact on cost-

Overall, this method seems feasible to implement but critically important normative questions remain regarding whether it is advisable to apply this kind of modification only for SSTs. Another remaining issue is whether it should matter whether the health care services whose costs are prevented (or unrelated future health care costs that may be incurred) by a successful SST are cost-effective themselves or whether they are priced at a level above the applicable incremental cost-effectiveness threshold. We opted not to test a strategy in which "best supportive care" is repriced in the model at a cost-effective level (i.e. <$150,000 per year) before calculating the cost offset from a new SST. To re-price all services in a model was viewed as time consuming and it is not clear that doing so would obviate the general concern about the magnitude of value-based pricing for a treatment such as a cure for hemophilia A, when many years of cost offsets, even if limited to $150,000 per year, would represent a tremendous sum.

Yet another issue unaddressed by these empirical tests is how to set an "appropriate" level for shared saving, and whether that level should be consistent across SSTs or dependent upon other considerations such as the magnitude of the value-based price, the cost of current treatment, and uncertainty over the magnitude of the cost-offset. It could be imagined that certain criteria would suggest higher levels, such as significant federal funding for the basic research underlying the SST.

The loss-of-exclusivity shared savings scenario could be considered especially relevant for SSTs, as their novel nature may lead to situations in which these treatments are less likely to face competition in the marketplace and thus may face little downward pressure on price over time.[36,76-80] As Towse and Fenwick have recently pointed out, there may be reduced gains to payers from competitive entry and loss of exclusivity for SSTs relative to chronic treatments.[75]

6. Discussion & Conclusions

In this paper, we have attempted to address key questions around the pricing and value of SSTs by bringing stakeholders and leading international health technology assessment agencies together to seek input on approaches to the evaluation of SSTs. We used a literature review and the stakeholder input to guide the development and testing of alternative methods for value-based pricing of SSTs.

The results from the literature review and our interviews informed the conceptual development of alternative methods to address the key methodologic and policy questions that frame this effort. We looked for precedent from international health technology organizations for potential adaptations and to the literature for methods to incorporate adaptations into test models. Those methods that were captured in the interviews and literature review, and had precedent and validated methodological approaches, were incorporated into various cure scenarios to determine the impact on value-based pricing estimates. We then selected from among these proposed methods those which were considered feasible and useful for testing in empirical analyses using previously developed models.

The aim of this testing was to explore the impact of different modeling approaches that might be considered for assessing potential cures, and their impact on estimates of the cost-effectiveness of these therapies in different disorders. Our approach was to use adaptations to three previously developed cost-effectiveness models that had been developed in collaboration with ICER's modeling network as part of previous assessments, evaluating treatments for SMA, hemophilia A, and B-cell lymphoma. Results were evaluated using several criteria, including face validity, the presence of ceiling/floor effects, the magnitude of change in results, and variation across different types of cure scenarios.

Increased Uncertainty with Unrecoverable Costs

The use of alternative plausible scenarios in cost-effectiveness models as part of an assessment seems feasible. However, the determination of the inputs and assumptions to be used in these scenarios will be critical to provide meaningful information on the uncertainty surrounding a new intervention. It would also be important for these scenarios to be informed by clinical expert opinion, as well as information from manufacturers and patients, and for the plausibility of these scenarios to be checked as more data become available.

The use of cure fraction models may better fit survival data in certain cases and may be especially relevant for SSTs. Testing different survival analytic techniques to provide the best fit to the available evidence will be key when trying to extrapolate long-term outcomes, but may require further assumptions about the curative effect of SSTs over the long-term.

The use of different probability filters at specific willingness-to-pay thresholds to constrain the value-based price range is feasible in practice and would likely result in narrower value-based price ranges, dependent on the specific likelihood filters selected. Limitations of this method are the potentially high resource demands of additional probabilistic sensitivity analyses and the sensitivity of results to the specific distributions and correlations used as inputs for the simulations.

Additional Dimensions of Value

We did not perform any empirical analyses for additional dimensions of value such as insurance value or the "value of hope" due to lack of required data. Further research into the methods and data required for these analyses are needed before their routine inclusion in cost-effectiveness analyses. However, these additional dimensions of value may be important to consider explicitly in the assessment of SSTs in a qualitative manner until quantitative analyses are available.

Time Divergence Between Costs and Benefits

The use of various discount rates or differential rates may lead to more favorable results for SSTs in some cases. For treatments with a one-time up-front cost, changes in the discount rate can have a larger impact on outcomes (which are streamed over time) than on costs (which are concentrated in the present), and therefore may have large impacts on estimated cost-effectiveness ratios. However, the basis on which to choose other discount rates is not clear, and the use of different discounting schemes for different types of conditions or interventions, such as SSTs, would make it more difficult to compare cost-effectiveness across intervention types.

Affordability and Fair Sharing of Economic Surplus

Reducing cost offsets captured in the net costs of interventions would lead to lower value-based prices at a given willingness-to-pay threshold, while still capturing the benefits from large health gains from these treatments as part of that price. However, it is unclear what the appropriate method would be to determine the level at which the assumed cost offset should be set. Any specific level selected may be considered arbitrary or unfair to a given stakeholder and may lead to concerns over its impact on the level of innovation over time. Finally, it may be considered unfair to treat cost offsets differently for SSTs than for other treatments simply because they have high value-based prices using conventional cost-effectiveness methods.

Conclusion

This draft technical brief outlines the conceptual development of a menu of methods options and the results of our empirical analyses and their application in various cure scenarios. We hope that this technical brief can serve as a foundation to spur discussion among researchers, insurers, life sciences companies, and policymakers to find ways to support innovation without financially crippling the health care system. There is no "silver bullet" solution, and it will require engagement from all stakeholders to help address the challenges our health care system faces in evaluating and pricing SSTs in a manner that will ultimately prove affordable and sustainable.

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Appendices

Appendix A: Interviews and Public Process

Interviews and Public Process

To help guide the parameters of our literature search, we conducted interviews of key stakeholders, both domestically and internationally. We targeted interviews domestically to include manufacturers with SSTs as well as relevant patient groups and payer organizations. We also conducted interviews of health economists and experts in health technology assessment domestically and internationally to learn from their expertise on why and how SSTs might be considered methodologically different from standard treatments. Finally, we held a four-week open input period to solicit guidance from interested stakeholders on methodological adaptations for SSTs.

Table A1. Summary of Open Input Responses by Commenter Affiliation

Commenter Type	Count of Commenter Type
Pharmaceutical Company	11
Industry Trade Group	5
Consultant	3
Patient Group	3
Economist	2
Grand Total	24

Table A2. Summary of Comments Received in Open Input

Comment Summary	# of Comments Recommending Approach:
Incorporate Societal Burden into or alongside base case	13
Incorporate caregiver burden	12
Present different scenarios to test assumptions around treatment effect and durability based on available data	10
Lower the discount rate, or try differential discount rates for costs and benefits.	8
Change (increase) WTP thresholds based on value criteria unique to cures	8
Tolerate more uncertainty; present ranges based on sensitivity analysis; and present variance and/or confidence intervals.	7
Model additional dimensions of value based on the ISPOR Value Flower (insurance value, scientific spillovers, etc.). Most cited 'petals' included equity, severity of disease, value of hope; followed by scientific spillover, insurance value, and real options value.	7
Employ techniques such as cure fraction modeling and survival models to understand patient level effects.	6
Formally incorporate a structure for re-evaluation as more data becomes available.	6
Financing and contracting mechanisms can manage uncertainty.	6
Recognize the psychological benefits of a complete cure.	6
Present the full cost-effectiveness analysis with no special advantages to cures or alterations to understand cost offset.	6
Test varying time horizons based on the availability of data.	5
Multi Criteria Decision Analysis or augmented CEA.	5
Weight the QALY to demonstrate additional elements of value.	4
Measure value separate from affordability.	4
Design policy options around level of uncertainty and plan to collect data, and link improvement in price to improvement in certainty.	3
Utilities should be from patient-centered research.	3
Incorporate impact on taxpayers and public programs.	3
Analyses with patient level data (matched adjusted indirect treatment comparisons, and simulated treatment comparison) or subgroup analyses.	3
Recognize the benefits of a cure reducing reinfection and/or genetic inherited diseases.	3
Present probabilistic sensitivity analyses to understand uncertainty.	2
Test varying scenarios with varying durability to understand the price at which a treatment is cost effective at varying endpoints.	2
To understand how cost offsets impact our analysis, alter the comparators and compare against best supportive care as well as next best alternative treatment.	2
There should be a threshold for when the value based price triggers financing decision.	2
Consider that the procedure will become more effective, safe and efficient as it becomes more widespread.	2
Consider including a summary value rating (in the same way we have an evidence rating).	1
Budget Impact trigger: No change in cost-effectiveness analysis. But budget impact may act as a mechanism to address affordability.	1
Test multiple scenarios around budget impact analysis (i.e. potential variability in our estimate of budget impact threshold).	1
Specify in advance the list of potential benefits of cures that will be considered	1
Consider alternatives to the QALY and EQ-5D, such as E-QALY	1
Explicitly break out costs to the health system (PBMs, pharmacies, etc.) outside of payer in our reports.	1

Table A3. Interviewees and Collaborators

U.S.-based and International Health Economists		
Lou	Garrison	University of Washington School of Pharmacy
Sean	Sullivan	University of Washington School of Pharmacy
Mark	Sculpher	University of York
Mike	Drummond	University of York
Chris	McCabe	Institute of Health Economics
Josh	Carlson	U of W
Jon	Campbell	U of Colorado - Denver
Matt	Stevenson	U of Sheffield
Nick	Crabb	NICE
Karen	Lee	CADTH
Lonneke	Timmers	Zoorginstituut
U.S. Stakeholder Groups		
John	Watkins	Premera Blue Cross
Chris	Leibman	Biogen
Tim	Hunt	Editas
Paul	Melmeyer	National Organization Rare Diseases
Annie	Kennedy	Parent Project Muscular Dystrophy
Tanisha	Carino	FasterCures
Morrie	Ruffin	Alliance for Regenerative Medicine
Geoffrey	Lomax	California Institute for Regenerative Medicine

Appendix B: Systematic Review

A literature review was conducted to address four key methodologic and policy questions that frame this effort. To help guide the parameters of our literature search, we conducted interviews of key stakeholders, both in the US and internationally.

Data Sources and Searches

We conducted the literature review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[81] The PRISMA guidelines include a checklist of 27 items, described further in Appendix Table A1.

For the literature review, we searched MEDLINE, EMBASE, Health Technology Assessment (HTA) Database, NHS Economic Evaluation Database (NHS EED), and the Cost Effectiveness Analysis (CEA) Registry. Each search was limited to English-language studies of human subjects and included articles from December 2004 until February 2019 indexed as full text, as well as letters, editorials, reviews, reports, or guidelines. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms, and are presented in Appendix Tables A2 and A3. To supplement the database searches, we performed manual checks of the reference lists of studies and interviewed key stakeholders with the aim of identifying any unpublished studies. We also supplemented our review of published studies with relevant data from conference proceedings. Search was performed using relevant terms on conference websites.

Study Selection

Study selection was accomplished through two levels of screening, at the abstract and full-text level. Citations accepted during abstract-level screening were retrieved in full text for review. Two reviewers independently screened the titles and abstracts of all publications and resolved any issues of disagreement through consensus or by consultation with a third reviewer.

Data Extraction and Quality Assessment

Data were extracted into evidence tables (Appendix Tables A4). Data extraction was performed in the following steps. First, four reviewers extracted data from the articles. Second, if there were any discrepancies, extracted data were reviewed for logic and validated by two reviewers for additional quality assurance. However, the methodological quality of included studies was not a formal part of this review due to the heterogeneity of the included studies.

Table B1. PRISMA 2009 Checklist

	#	Checklist item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.

Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Figure B1. PRISMA Flow Chart

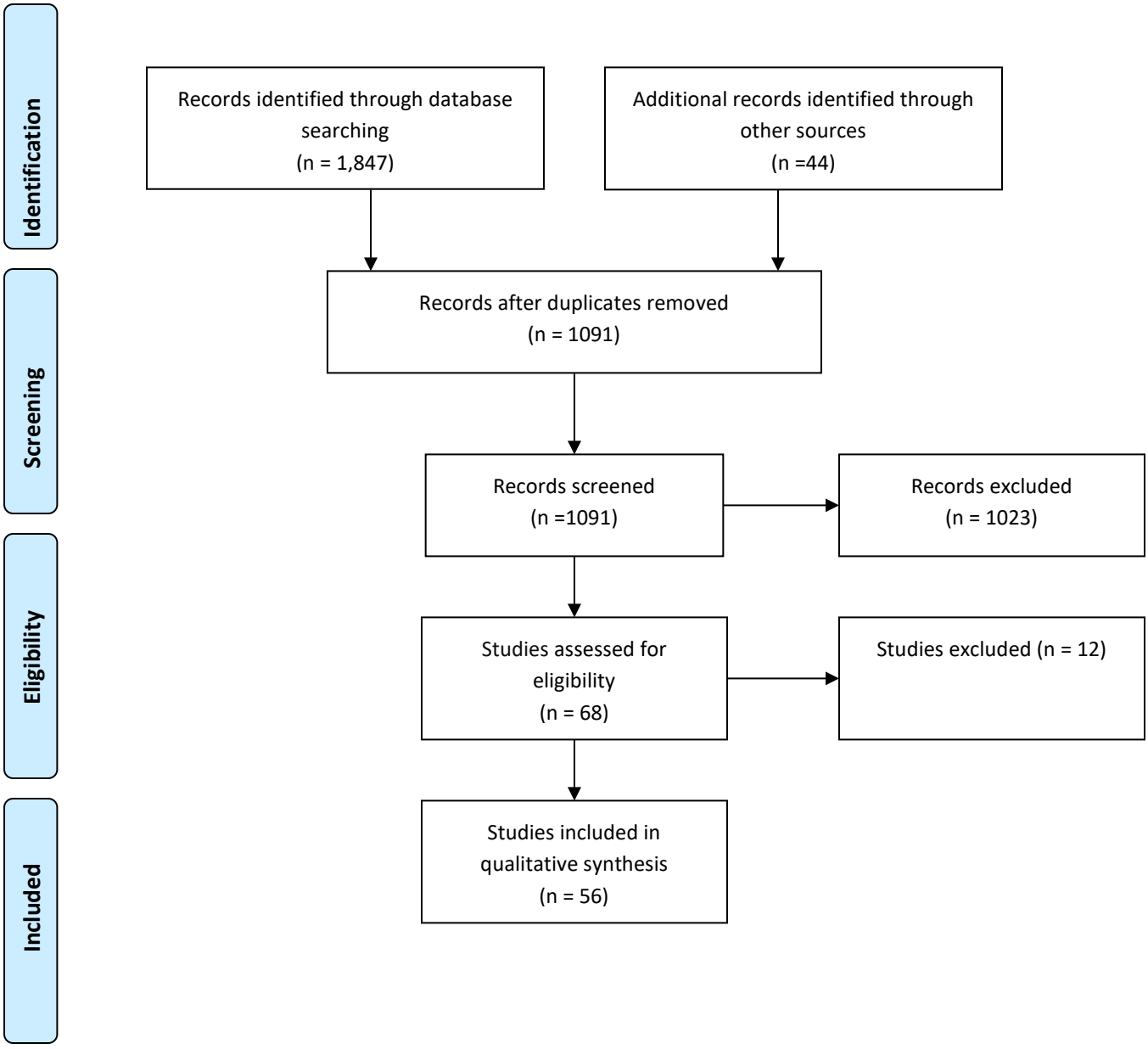

Table B2. Search Strategy of MEDLINE from 2004 until 2019

1	cure:ti,ab OR 'gen* therap*':ti,ab OR 'dna therap*':ti,ab OR ((regenerative NEAR/1 (therap* OR medicin*)):ti,ab) OR 'regenerative medicine'/exp OR 'regenerative medicine' OR 'cell* therap*':ti,ab OR 'tissue* therap*':ti,ab OR 'curative therap*':ti,ab
2	(price:ti,ab OR value:ti,ab OR 'economic evaluation'/exp OR ((economic* NEAR/1 evaluation):ti,ab) OR ((cost* NEAR/1 effectiv*):ti,ab) OR ((cost* NEAR/1 utilit*):ti,ab) OR ((budget NEAR/1 impact):ti,ab)) AND method*:ti,ab
3	#1 AND #2
4	#3 AND [medline]/lim
5	#4 AND [2004-2019]/py AND [english]/lim
6	#5 AND 'human'/de

Table B3. Search Strategy of EMBASE from 2004 until 2019

1	('cure'/exp OR 'cure' OR 'curative')
2	('gene* therap*' OR 'dna therap*' OR '(cell and tissue*) therap*' OR 'regenerative' OR 'regener*') AND 'therap* OR medicin*'
3	1 OR 2
4	(price and meth*)' OR '(value or value based) price' OR 'econ* and evaluation' OR 'cost and effective*' OR '(cost and effective*) price' OR (cost AND effect* AND price) OR 'cost and utility' OR (cost AND utili*) OR '(value and value based) meth*' OR '(cost and meth*) and (budget and impact) meth*'
5	3 AND 4
6	5 AND [embase]/lim
7	6 AND [2004-2019]/py AND [english]/lim AND 'human'/de

Table B4: Evidence table of the included studies

Source	Key methodological and policy questions
Q1	**How should value-based prices for potential cures reflect substantial uncertainty regarding clinical safety and effectiveness due to limitations in study design, outcome measures, and the size and duration of clinical trials?**
The assessment and appraisal of regenerative medicines and cell therapy products: an exploration of methods for review, economic evaluation and appraisal. ***Hettle et al, 2017[11]***	The National Institute for Health and Care Excellence (NICE) commissioned a 'mock technology appraisal' to assess whether changes to its methods and processes are needed. This report presents the findings of independent research commissioned to inform this appraisal and the deliberations of a panel convened by NICE to evaluate the mock appraisal. The findings of the report indicate that it is to be expected that there will be a significant level of uncertainty in determining the clinical effectiveness of regenerative medicines and their long-term costs and benefits, but the existing methods available to estimate the implications of this uncertainty are sufficient. The use of risk sharing agreements between the NHS and manufacturers of regenerative medicines should be investigated further.
Exploring the Assessment and Appraisal of Regenerative Medicines and Cell Therapy Products: Is the NICE Approach Fit for Purpose? ***Marsden G and Towse A, 2017[82]***	The purpose of this report is to review and summarize the NICE's CAR-T exercise and to assess whether or not the resulting conclusions are appropriate.
Evaluating and valuing drugs for rare conditions: No easy answers. ***Ollendorf DA, Chapman RH, Pearson SD, 2018 [83]***	In this paper, the authors explore the general ethical dilemmas that rare diseases present, steps taken by health technology assessment bodies worldwide to define the level of rarity that would necessitate special measures and the modifications to their assessment and valuation processes needed, and the contextual components for rare-disease evaluation that lie outside of the assessment framework as a guide to US decision makers on constructing a formal and relevant process stateside.
Small Clinical Trials: Issues and Challenges, Institute of Medicine, 2001[84]	This report assesses the published literature on various strategies such as (1) meta-analysis to combine disparate information from several studies including Bayesian techniques as in the confidence profile method and (2) other alternatives such as assessing therapeutic results in a single treated population (e.g., astronauts) by sequentially measuring whether the intervention is falling above or below a preestablished probability outcome range and meeting predesigned specifications as opposed to incremental improvement
The ethics of clinical trials ***Nardini C, 2014. [85]***	In this review, the author discusses some of the most important ethical issues surrounding RCTs, with an eye to the most recent debates and the context of oncological research in particular.

Gene therapy: evidence, value and affordability in the US health care system. Hampson G et al, 2018[6]	This paper explores the challenges presented by gene therapies, discuss potential solutions, and present policy recommendations.
Accounting for Cured Patients in Cost-Effectiveness Analysis. Othus et al, 2017[37]	This paper aims to explain how to incorporate the heterogeneity from cured patients into health economic evaluation by analyzing clinical trial data from patients with advanced melanoma treated with ipilimumab versus glycoprotein 100 with statistical methodology for mixture cure models
Projecting survival with cure mixture models: when are the data mature enough for reliable analysis? Ishak et al, 2018[41]	This abstract highlights the risks of misleading projections with models that otherwise meet the usual evaluation criteria (e.g., fit statistics, close prediction of the data). The shape of the extrapolation and the plausibility of the estimated cure fraction are critical with these methods.
Joint Committee on Vaccination And Immunisation, Code of Practice June 2013[47]	The Joint Committee on Vaccination and Immunization code of practice states adjustment factors should be applied to modelled benefits or costs when there is good reason to believe that these are underestimated or overestimated and that the incremental cost effectiveness ratio should then be judged against a £20 000 threshold per QALY.
Advanced therapy medicinal products and health technology assessment principles and practices for value-based and sustainable healthcare. Jonsson et al, 2019[86]	This paper identifies and discusses potential challenges of Advanced therapy medicinal products (ATMPs) in view of current health technology assessment methodology-specifically economic evaluation methods-in Europe as it relates to ATMPs, and to suggest potential solutions to these challenges.
Discounting in Economic Evaluations. Attema et al, 2018[31]	In this article, the authors review the debates around discounting, and describe and discuss the current discounting recommendations of the countries publishing their national guidelines.
Tiered and flexible pricing strategies in the pharma industry Accessed May 5, 2019 https://ihsmarkit.com/research-analysis/q13-tiered-and-flexible-pricing-strategies-in-the-pharma-industry.html[87]	This interview is about tiered and flexible pricing strategies in the pharma industry.
Objectives, Budgets, Thresholds, and Opportunity Costs-A Health Economics Approach: An ISPOR Special Task Force Report [4]. Danzon et al, 2018[88]	The fourth section of the Special Task Force report focuses on a health plan or payer's technology adoption or reimbursement decision, given the array of technologies, on the basis of their different values and costs. The report discusses the role of budgets, thresholds, opportunity costs, and affordability in making decisions.

Evidence-Based Decision Making: When Should We Wait for More Information? Chalkidou et al, 2008[89]	In this paper, the authors discuss the challenge of managing innovation in and access to health care interventions in an evidence-based, cost-effective way, and we describe a decision-making framework (using U.S. and U.K. case studies) for health care payers considering the adoption of new technologies. They argue that providing reimbursement for what could be a cost-effective technology "only in the context of research" will be appropriate if the costs of delaying implementation are offset by the value of "keeping one's options open" by waiting for more information.
Q2	How should value-based prices for potential cures reflect uncertainty regarding inclusion of additional elements of value that may be important for potential cures, but which are not part of standard cost-effectiveness methods?
Defining Elements of Value in Health Care-A Health Economics Approach: An ISPOR Special Task Force Report ***Lakdawalla et al. 2018***[21]	Authors identified eight additional elements of value. These additional elements of value include reduction in uncertainty, fear of contagion, insurance value, severity of disease, value of hope, real option value, equity, and scientific spillovers. Further research is needed on how best to measure and include these elements in decision-making.
Toward a Broader Concept of Value: Identifying and Defining Elements for an Expanded Cost-Effectiveness Analysis ***Garrison et al. 2017***[22]	Authors describe five factors related to the value of knowing: a reduction in uncertainty, reflecting the benefit of a companion diagnostic increasing the certainty of a patient's response to a medicine; insurance value related to greater peace of mind due to protection against a financial loss; the value of hope for a 'cure' leading individuals to become risk seekers in some circumstances; real option value due to life extension; and scientific spillovers. Further research is needed on how best to measure and include these factors in decision-making.
Advanced therapy medicinal products and health technology assessment principles and practices for value-based and sustainable healthcare ***Jönsson et al. 2018***[90]	The following additional elements of value were identified: disease severity, age of onset, lifetime burden of illness, socioeconomic impact, and possible spillovers from the initial innovation or improvements in the quality of or process of care that may not be captured by measures of improvements in health outcome.
How cancer patients value hope and the implications for cost-effectiveness assessments of high-cost cancer therapies ***Lakdawalla et al. 2012***[91]	Authors assessed the value of hope in cancer patients. This study suggests that most cancer patients may prefer a therapy with the possibility of a large survival gain, even if the therapy's average or median survival is similar to that of alternative therapies. Patients facing other fatal diseases might share such a preference; evidence from other contexts would be welcome in reinforcing and extending the base of evidence on this point. Authors suggested that CEAs should either incorporate hope into the value of therapies or set a higher threshold for an acceptable cost-effectiveness ratio in the end-of-life context.
The Insurance Value of Medical Innovation. Working Paper 21015.	Authors present an alternative framework that accounts for how innovation can lower physical risks borne by healthy patients facing the prospect of future disease and link this to the value of healthcare insurance. This study suggests that

Lakdawalla et al. 2015[92]	conventional methods meaningfully understate the value of historical health gains and disproportionately undervalue treatments for the most severe illnesses, where physical risk to consumers is the costliest. These calculations also suggest that the value of physical insurance from new technologies may exceed the financial spending risk that they pose.
Real option value and path dependence in oncology innovation ***Cook et al. 2011***[27]	Authors identified real option value as an additional element of value and argue policy makers should consider option value when rewarding innovation. It was stated that, NICE already uses option value in the pricing of drugs: it is option value that determines whether more research evidence is required before use of a technology is recommended (value-of-information approach). Although the issue of associating different option values with different development paths is taken into consideration in technology assessment, the way that NICE and other HTA bodies tackle this issue is not explicit.
The value of knowing and knowing the value: improving the health technology assessment of complementary diagnostics ***Garrison et al. 2016***[22]	Authors identified the following additional elements of value: reduction in uncertainty, value of hope, real option value - the value of benefiting from future technologies due to life extension, insurance value - psychic value provided by invention of an innovative medical product and by the accompanying financial risk protection afforded by a new treatment, scientific spillovers - value due to other innovations that become possible once a new technology has been proven to work.
Gene Therapy International Regulatory and Health Technology Assessment Activities and Reimbursement Status ***CADTH, 2018*** [93]	The methodological modifications suggested in this report include presenting the scale of decision uncertainty using population-level health effects; formally considering irrecoverable costs; and considering the impact of learning curves for clinical and cost-effectiveness assessments.
Objectives, Budgets, Thresholds, and Opportunity Costs-A Health Economics Approach: An ISPOR Special Task Force Report ***Danzon, Drummond, Towse, Pauly, 2018***[88]	If novel elements of value are added to the QALY measure of health gain, with no change in the budget, the threshold would need to be reduced because the average measured benefit of technologies would increase. Authors indicated that to reflect society's view, in some circumstances, health gain at the end of life is worth more to individuals than at other points in their lives.
Valuing a cure: Are new approaches needed? ***Grueger* 2018**[94]	In this presentation, value of hope is identified as an additional element of value.
Theoretical models of the cost-effectiveness threshold, value assessment, and health care system sustainability ***Pandey, Paulden, McCabe, 2018.***[95]	A societal preference for placing additional value on treatments for severe conditions, conditions for which there is no current therapy, and high cost/catastrophic cost treatments appeared to be consistent across studies - but this is not ready for quantitative analysis, important qualitatively to consider horizontal vs. vertical equity.

The Value of Innovation. Report by the Decision Support Unit ***Claxton et al. 2009*** [96]	Authors question of how to value innovation and how to ensure that there are sufficient incentives for private investment in the development of socially desirable innovations requires a clear view of the social value of a health technology, its relationship to price, and the incentives this provides for private sector investment decisions.
Regenerative Therapies: Are We Ready for a Cure? Key Value and Policy Considerations to Facilitate Access ***Thomas, 2017***[97]	Potential avoidance of the burden of medication nonadherence seen with chronic therapies and medication wastage.
The Value of Innovation in Oncology: Recognizing Emerging Benefits Over Time ***Sweeney N and Goss T, 2015.***[98]	Additional element of value is recognized through a number of pathways, including: • Use within a singular FDA-approved indication • Use earlier in treatment line and in earlier disease stage • Use in different disease indications • Use in combination with other agents • Use in combination with specific biomarkers These pathways may provide a framework for a better understanding of the true clinical value of a therapy over time.
Drug development and public research funding: evidence of lagged effects ***Blume-Kohout M. 2009.***[26]	Economists have empirically documented the causal effect of early innovation on future breakthroughs using the National Institutes of Health funding as a natural experiment and clinical trial starts as an outcome. This study shows that measures of innovation outcomes and compelling empirical identification of causal increases in 'original' innovation are not straightforward.
IVI NSCLC model ***Innovation and Value Initiative, 2019*** [99]	Value of hope is incorporated into economic analyses of non-small cell lung cancer therapies. IVI's definition of 'value of hope' is the difference between expected incremental QALYs (based on the mean benefit) and the certainty equivalent. And the certainty equivalent is the number of QALYs that a patient would need to obtain to be indifferent between the comparator and an alternative treatment strategy, in light of the alternative's distribution of survival outcomes.
IVI RA model ***Innovation and Value Initiative, 2019*** [100]	Insurance value is incorporated into the economic analyses of Rheumatoid Arthritis therapies. Calculating this value requires data on marginal rate of substitution (MRS) between sick and healthy states. In the IVI's model, this MRS is set to 1.5, with the authors acknowledging considerable uncertainty around this estimate. There is no robust evidence regarding IVI's insurance value inputs.
The option value of innovation ***Snider et al. 2012***[29]	Real option value is estimated by accounting projected increases in survival using established forecasting models. Authors provide a proof-of-concept study using the example of the drug tamoxifen. They find that incorporating option value can increase the conventionally estimated value of tamoxifen with better adjuvant treatment by nearly a quarter (from $200,000 to $248,000). Authors indicated that they expect similar results for other drugs in therapeutic areas of rapid technological advancement.

Q3	How should value-based prices for potential cures reflect extreme magnitudes of lifetime health gains and cost offsets that are far beyond those generated by traditional therapies?
The Value of Innovation. Report by the Decision Support Unit Claxton et al[96]	The aim of this review is to provide an overview of how innovation is currently valued in the UK health system and the potential initiatives that can be adopted in order to promote innovation in the National Health System.
When is it too expensive? Cost-effectiveness thresholds and health care decision-making Brouwer et al[70]	In this editorial, the authors focus on the question of how a line should be drawn beyond which a technology is considered to be too expensive, and therefore, should not be reimbursed. They argue that if health economic evaluations are to have more impact on decision-making, interactions with decision makers and the public are required to bridge the gap between academic endeavors and societal and political realities.
Financing cures in the United States. Basu A[101]	In this paper, the author proposes a new health currency as a generalized version of a social impact bond that has the potential to solve the free-rider problem, where no one health plan has the incentive to invest in cure since the returns will be scattered over many health plans, as it can be traded not only between public and private payers but also within the private sector.
Financing a Cure for Diabetes in a Multipayer Environment. Basu et al[102]	In this paper, the authors develop the precise conditions needed for a financing mechanism, HealthCoin, to work between a private payer and Medicare, to incentivize the former to invest in breakthrough therapies or cures in the US by illustrating the valuation of such a currency for a cure of Type 2 diabetes.
Valuing a cure: Are new approaches needed? Grueger J[94]	In this presentation, the author discusses how to balance early access for treatments with high potential benefit with sufficient evidence.
Searching for a threshold, not setting one: the role of the National Institute for Health and Clinical Excellence. Culyer et al [103]	The authors discuss whether the National Institute for Health and Clinical Excellence (NICE) has, or ought to have, a 'threshold' figure for the cost of an additional quality-adjusted life-year above which a technology will not be recommended for use. They argue that it is not constitutionally appropriate for NICE to set such a threshold, which is properly the business of parliament. Instead, the task for NICE is as a 'threshold-searcher' - to seek to identify an optimal threshold incremental cost-effectiveness ratio, at the ruling rate of expenditure, that is consistent with the aim of the health service to maximize population health.
Q4	How should value-based prices reflect the disconnect between the time when expenses and benefits accrue?
Why the far-distant future should be discounted at its lowest possible rate. Martin Weitzman[104]	This paper shows that there is a well-defined sense in which the ‘‘lowest possible’’ interest rate should be used for discounting the far-distant future part of any investment project. Some implications are discussed for evaluating long-term environmental projects or activities, like measures to mitigate the possible effects of global climate change.

Discounting the Recommendations of the Second Panel on Cost-Effectiveness in Health and Medicine. ***Paulden et al[32]***	The purpose of this paper is to critique the second panel's updated guidance regarding the discounting of costs and health effects. The advances in discounting methodology since the first panel include greater theoretical clarity regarding the specification of discount rates, how these rates vary with the analytical perspective chosen, and whether the healthcare budget is constrained.
Discounting health outcomes in economic evaluation: the ongoing debate ***Severens and Milne[33]***	The purposes of this paper are: to outline the theoretical arguments regarding uniform or differential discounting; to provide an overview of the empiric evidence supporting or opposing both methods; to consider time-varying discounting; and to formulate interim recommendations.
The practice of discounting in economic evaluations of healthcare interventions ***Smith and Gravelle[64]***	The authors sought to explore the current recommendations and practice in health economic evaluations with regard to discounting of costs and benefits by surveying recommendations for best practice on discounting for health effects as set out by government agencies, regulatory bodies, learned journals, and leading health economics texts
Foundations of cost-effectiveness analysis for health and medical practices ***Weinstein and Stason[65]***	The paper focuses on the main aspect of cost-effectiveness analysis and discusses limits on health-care resources, quality-of-life concerns, the timing of future benefits and costs and the analyses that should be adaptable to the needs of various health-care decision makers, including planners, administrators and providers.
Discounting of Life-Saving and Other Nonmonetary Effects ***Keeler and Cretin [66]***	This paper presents an argument for the equality of the discount rates when hard to monetize benefits such as life-saving are involved. It shows that if the ability to produce the nonmonetary effect does not diminish too quickly over time, failure to discount benefits implies that programs are always improved by delay.
Economic evaluation in health care: merging theory with practice ***Drummond and McGuire[105]***	This book provides an in-depth discussion of the latest theoretical advances and gives a comprehensive review of the available literature.
Theoretical arguments for the discounting of health consequences: where do we go from here? ***Lazaro[67]***	The paper argues that the relationship between the discount of monetary and health consequences must be determined in an indirect manner, by reference to the relationship maintained by the individual time preference rates for health and money in the context of private and social choice.
Advocating a paradigm shift in health-state valuations: the estimation of time-preference corrected QALY tariffs ***Jonker et al[106]***	The aim of this study was to introduce a general method of accommodating for nonlinear time preferences in discrete choice experiment duration studies and to evaluate its impact on estimated QALY tariffs.
Methods of international health technology assessment agencies for economic evaluations-a comparative analysis ***Mathes et al [50]***	The objective of this paper is to provide an overview and comparison of the methodological recommendations of international HTA agencies for economic evaluations by presenting a detailed analysis of existing similarities and differences in recommendations to identify potential for harmonization.

Spanish recommendations on economic evaluation of health technologies López-Bastida et al[51]	The objective of this proposal was to develop guidelines for the economic evaluation of health technologies in Spain. A group of researchers specialized in economic evaluation of health technologies developed the report to provide recommendations for the standardization of methodology applicable to economic evaluation of health technologies in Spain.
National Institute for Health and Care Excellence: Guide to the Methods of Technology Appraisal[43]	The purpose of this document is to provide an overview of the principles and methods of health technology assessment and appraisal within the context of the NICE appraisal process. It describes key principles of appraisal methodology and is a guide for all organizations considering submitting evidence to the technology appraisal program of the Institute.
Guidelines for economic evaluations in Italy: recommendations from the Italian group of pharmacoeconomic studies Capri et al[53]	This article reports the Italian Group for Pharmacoeconomic Studies' main recommendations, highlighting the most relevant theoretical and practical issues which could be useful for the regulatory authorities of the ministries involved, the Italian National Health Service people responsible at various levels for financing, administrators of medical structures, and pharmaceutical companies.
Guidelines for the Economic Evaluation of Health Technologies in Ireland 2010[55]	This guideline is part of the series of guidelines that also includes the Guidelines for Budget Impact Analysis of Health Technologies in Ireland (2014) and the Guidelines for Evaluating the Clinical Effectiveness of Health Technologies in Ireland (2011). This document is limited to methodological guidance on the conduct of economic assessments.
Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra, 2008[107]	The PBAC Guidelines explain in detail how to prepare a submission to list a new medicine or medicinal product on the Pharmaceutical Benefits Schedule (i.e., for public funding). The guidelines provide detailed instructions on what information is required by the PBAC and the Economic Sub-Committee (ESC) to support a proposed new medicine, and the most appropriate form of clinical evidence and economic evaluation for specific submissions.
Prescription for Pharmacoeconomic Analysis. New Zealand: PHARMAC, 2007[108]	The *Prescription for Pharmacoeconomic Analysis* (PFPA) is a guide for anyone assessing the value for money of pharmaceuticals in New Zealand. The intention is that funding proposals can be assessed to common standards, to support the best possible comparison between proposals. The PFPA may be useful for applicants submitting funding applications to PHARMAC, whether for medicines (which includes vaccines and some hemophilia treatments) or medical devices.
Guidelines for Economic Drug Evaluation Studies. Portugal:INFARMED, 1998[109]	This publication is the result of methodical work that began with the realization of the need for better information in drug evaluation in Portugal. Information and the ways of obtaining it were then systematized and group of outside experts was formed to provide technical and scientific support for the preparation of the methodologies. These methodologies were then adopted under the law for systematic application.
Canadian Agency for Drugs and Technologies in Health. Guidelines for the Economic Evaluation of Health Technologies: Canada. Canada: CADTH, 2006[110]	The guidelines detail best practices for conducting economic evaluations. They reflect current practices and promote the use of high-quality economic evaluations to inform health care decision-making. In particular, the guidelines are intended to help produce credible and standardized economic information that is relevant and useful to decision-makers in Canada's public health care system.

Agency for Health Technology Assessment: Guidelines for Conducting Health Technology Assessment (HTA) Economic Analysis. Agency for Health Technology Assessment, Warsaw (2009)[99]	The purpose of these Guidelines for conducting Health Technology Assessment is to indicate the principles and acceptable methods of performing Health Technology Assessment to ensure high quality of analyses and reliable results in Poland.
Belgian guidelines for economic evaluations and budget impact analyses. Health Technology Assessment (HTA) Brussels: Belgian Health Care Knowledge Centre (KCE). 2012.[62]	The objective of this study was to develop methodological and reporting guidelines for economic evaluations and budget impact analyses of medical interventions, be it pharmaceutical, medical device or other interventions, submitted to expert committees advising the health minister about reimbursement in Belgium.
ZorgInstituut Nederland (ZIN). Guideline for economic evaluations in healthcare. Diemen. 2016.[63]	This new guideline unifies all previously available Dutch guidelines, links up with international developments, provides unambiguous instructions and is broadly applicable, not only to pharmaceutical care. The Guideline is intended for those who perform economic evaluations to inform decisions on whether new healthcare interventions should be implemented or existing interventions that should be discontinued.

Appendix C: Overview of Methods Considered

Methods Key:
Red: We are no longer considering this method
Blue: We are actively considering this approach
Green: We have selected this approach for valuing potential cures

Concept	Key Questions	What are Technical Aspects to this Approach?
Background/Goals of Assessment		
Justification for Alternative Methods for Potential Cures	Why are we considering alternative methods for potential cures?	• The disjunction of the cost and the benefit • the potential magnitude of the health benefit and/or cost offsets raises concerns about applicability and cost effectiveness • heightened uncertainty about the durability of treatment effect • potential other elements of value uniquely relevant for cures

Definition of a Potential Cure	Which treatments would we treat with this methodology for potential cures?	• A one-time or short-term treatment that achieves one of the following:
		  • Absence of disease or condition and restoration of normal health over the intermediate-term for a substantial proportion of patients treated, with promise that these patients will have lifelong durability of effects; or
		  • Halt of decline over the intermediate-term among patients with a progressively worsening condition, with promise that the condition will be stabilized without further deterioration for the lifetime of the patient
		• Substantial gain in life years
		• Consider alternative terminology: short term treatment with the potential for long term health gain

Concept	Key Questions	What are Technical Aspects to this Approach?
Measuring and Describing Uncertainty		

Adjusting ICERs for Relative Uncertainty	How does the presentation of uncertainty relate to our determinations of value based prices?	• We will present plausible conservative, base case, and optimistic scenarios:
		  o **Basecase**: Present same basecase as in the initial report.
		  o **Conservative**: Based on discussion with clinical experts and the availability of evidence, we will identify aspects of the model, such as the durability & magnitude of effect, proportion of benefit, and natural history of similar treatments, to consider the most plausible conservative option.
		  o **Optimistic**: Based on discussion with clinical experts and the availability of evidence, we will identify aspects of the model, such as durability & magnitude of effect, proportion of benefit, and natural history of similar treatments, to consider the most plausible optimistic option.
		• Panel will be presented with all results and will continue to have a single vote on value with deliberation on which scenario seems to be the most plausible.
		• If the uncertainty is of a certain magnitude, we will link to specific policy recommendations (such as outcomes based arrangements)
		• Base case will be determined such that 50% of PSA simulations are below 150K/QALY and 90% of PSA simulations are under 250k/QALY.

Empirical Approaches to Capturing Uncertainty about Longer-Term Safety and Effectiveness	How do you empirically capture uncertainty in determining value based pricing?	• To evaluate uncertainty, consideration will be given to:
		  • Cure fraction models (req. patient-level data or assumptions);
		  • Spline-based survival models
		• Threshold analysis for durability of effects when price known

Concept	Key Questions	What are Technical Aspects to this Approach?
		• Perform analyses for lifetime and the horizon that matches the longest duration of existing evidence • Model averaging (structural uncertainty) • Present information on whether manufacturers have long-term outcomes data collection plan
Dimensions of Value		
QALY	Should the QALY be weighted higher or lower in a systematic fashion?	• NICE HST additional QALY weights for QALY gains >10 • Apply proportional QALY shortfall in the reference case • Apply absolute QALY shortfall in the reference case
Utility Weighting	Patients facing life threatening illness may be more risk seeking	• When a choice of utilities are available, preference will be to standard gamble from patient population
Additional Dimensions of Value	Are there additional dimensions of value that may be considered for potential cures?	• Explore empirical approaches to modeling insurance value and scientific spillovers as scenarios
Other Benefits/Contextual Considerations		
Other Benefits and Disadvantages	Trial dosing may not be optimal but preclude future treatment (Ab)	• Add question: If not a cure, treatment would preclude or reduce chance of effectiveness of future treatments.
Contextual Considerations	Will a learning curve impact safety and effectiveness?	• Add a question: procedural uncertainty
Valuing Large QALY Gains and Cost Offsets		
Very High QALYs and Cost Offsets Suggesting	Are there principles guiding shared surplus between the innovator versus society?	• Set the return to the innovator to match profit in other types of treatments • Use criteria to assign a specific proportion of the cost offset to the innovator versus society

Concept	Key Questions	What are Technical Aspects to this Approach?
Very High Value-Based Prices		• Compare against best supportive care • Option 1: No change. Use potential budget impact as a mechanism to address short term affordability. • Option 2: Full QALY/evLYG valuation. Reprice cost offset to cost-effective levels, then full valuation. • Option 3: Full QALY/evLYG valuation. If cost offset >$10 million, then share 50% of cost offset with society • Option 4: Set cost offsets to 0 after 12 years of exclusivity to represent average duration of patent life.
Other		
Societal Perspective	Should we think about the societal perspective differently for potential cures?	• Adopt the same language from URD: *When the impact of treatment on patient and caregiver productivity, education, disability, and nursing home costs is substantial and these costs are large in relation to health care costs, ICER will present in its basecase health system perspective model results in tandem with the results of a scenario analysis inclusive of broader societal costs. Similarly, a value based price benchmark (VBPB) linked to the societal perspective analysis will be presented alongside the standard VBPB.*
Lifetime Costs	Patients who are 'cured' will continue to incur health care costs over their lifetime.	• In all scenarios, we will present a lifetime average of health care costs for 'saved' lives.
Modeling the impact of Disease Recurrence	Some cures for infectious disease may raise questions about rates of potential re-infection; a potential cure for an infectious disease may also have potential for reduced infection with infectious disease.	• Perform scenario analysis to model re-infection rates and public health perspectives

Concept	Key Questions	What are Technical Aspects to this Approach?
Discounting	Questions about the social value of health care and costs in the future	• Same discount rate for costs and effects, at varying levels • Lower discount rate for effects than for costs, at varying levels • Hyperbolic discount rate: 3% at first, and then following a curve • Discount rates to use in the above methods could include: o 0%, 1.5%, 3%
Broader Benefits to Wellbeing Outside the QALY	HTA captures immediate impact on QoL but not long-term improvements or changes in QoL or opportunity costs, dignity, respect (ability to grow up, go to college, have a family, etc.)	• Unknown if empirical methods exist
Unrelated Medical Costs	For treatments that halt decline in a progressive illness, but extend length with high related medical costs	• Scenario analysis with and without associated health care costs
Budget Impact Analyses		
Global Budget for All Drugs/Cures	Should we consider the impact of many potential cures approved within a short timeframe with high prices?	• Best approaches and perspectives for cumulative impact of treatment

Appendix D: Methods for Empirical Analyses

Approach

This analysis plan details our modeling approach as adaptations to three previously developed cost-effectiveness models. As part of our approach to valuing potential cures, we will select specific approaches to test, based on a systematic literature review of the evidence pertaining to valuing potential cures, as well as discussions with stakeholders in academia, health technology assessment, healthy policy, and payer organizations.

For these modeling adaptations, we have chosen the following three previously developed models developed in collaboration with ICER's modeling network as part of previous assessments:

1. B-Cell Lymphoma: Yescarta® (axicabtagene ciloleucel), a chimeric receptor antigen T-cell (CAR-T) therapy versus chemotherapy in adults with refractory aggressive B-cell lymphoma who are ineligible for autologous stem cell transplant.
2. Hemophilia A: A hypothetical one-time cure and a hypothetical long-term potential cure versus bypassing agents (BPA) in Hemophilia A patients with inhibitors
3. Spinal Muscular Atrophy (SMA) Type 1: Zolgensma (onasemnogene abeparvovec) versus best supportive care (BSC) in patients with Type 1 SMA

All model adaptations will follow the same time horizons, base case perspectives, and outcomes as the originally published cost-effectiveness analyses. For details on treatment efficacy, quality of life, and cost estimates, please refer to ICER's published reports on the therapies considered.

The aim of these analyses is to explore the impact of different modeling approaches that might be considered for assessing potential cures and their impact on estimates of the cost-effectiveness of these therapies in different diseases/disorders. All but one model adaptation analyses will be conducted in Microsoft Excel 2016 (Redmond, WA).

Methods

All modeling adaptations will be based on previously developed models built specifically for ICER reviews in three therapeutic areas for which transformative therapies potentially exist: B-cell lymphoma, Hemophilia A, and SMA. All analyses will take a health care sector perspective and thus will focus on direct medical care costs and outcomes alone.

All model adaptations will focus on intention-to-treat analyses with hypothetical patient cohorts being treated with relevant potential cures. In general, modeled time horizon, cycle lengths, clinical efficacy inputs, and cost inputs (except for the Hemophilia A hypothetical therapies) will be based on the relevant previously published ICER models. Since the aim of these analyses is to explore how

using different methodological approaches to valuing transformative therapies will impact cost-effectiveness outcomes, we will not use any updated clinical efficacy/effectiveness data or updated cost data in these model adaptions that may influence the differences in results between the model adaptations and the original models.

Below are the specific modeling methodologies we will consider in our adaptations when evaluating potential cures. The modifications presented below are structured in alignment with the four categories that form the framework for this project:

- Uncertainty
- Discounting
- Additional elements of value
- Magnitude of health gains and cost offsets

Uncertainty

1. Durability/Magnitude of Effect

Most trials evaluating the efficacy of transformative and/or potentially curative therapies are short-term, rendering long-term efficacy highly uncertain. To help account for this uncertainty, we will include three scenarios, as described below.

I. Base Case: The base case analysis will be the same as that of the final evidence report for each of the modeled therapies. In Hemophilia A, the base case was assumed to be the hypothetical therapies having the same health outcomes as for Hemlibra® (emicizumab) in that report; while we acknowledge that this does not represent a "cure," we include this base case for illustrative purposes. Costs of the long-term hypothetical therapy was also assumed to be the same as that of Hemlibra's. However, we assumed different costs for the one-time hypothetical gene therapy (SST), at $5 million and at $15 million (the lifetime discounted cost of Hemlibra as per the original base case analysis of Hemlibra). Below is a brief description of the previously conducted base case analysis for each of the three models. Unless otherwise specified below, all models discount cost and health outcomes using a 3% annual discount rate, over a lifetime time-horizon.
    a. B-cell Lymphoma – The aim of the original analysis was to estimate the cost-effectiveness of Yescarta® (axicabtagene ciloleucel), a chimeric receptor antigen T-cell (CAR-T) therapy versus chemotherapy in adults with refractory aggressive B-cell lymphoma who are ineligible for autologous stem cell transplant. A two-part partitioned survival model (short-term decision tree and long-term semi Markov model) was developed. Patient survival was calculated from available Kaplan-Meier survival curves from key trials which were digitized and extrapolated through five years after treatment initiation, at which point those alive and responding to treatment were considered effectively cured. After five years, those that were effectively cured exhibited mortality consistent with that of the general population.

Those alive and not cured at the end of the five-year period transitioned to palliative chemotherapy. The model adopts a monthly cycle length.

b. Hemophilia A – The aim of the original analysis was to estimate the cost-effectiveness of Hemlibra prophylaxis to two alternative strategies (BPA prophylaxis and no prophylaxis) in male patients with Hemophilia A with inhibitors to factor VIII who will not be treated with ITI or for whom ITI has been unsuccessful. Target populations comprised patients 12 years and above, and those under 12 years of age. For our modifications using the hypothetical Hemophilia A therapies, we will focus on the twelve years and over population. Our base case will model Hemlibra's effectiveness in reducing bleeds The Markov model included health states for individual bleed events as well as the development of joint arthropathy over time, with fewer joint bleeds over a lifetime leading to reduced levels of joint arthropathy. Patients entered the model based on the number of joints with arthropathy (0, 1, 2+) and from these sub-models transitioned from the "No Bleed" health state to "Untreated Bleeds", "Treated Bleed Not into a Target Joint" or "Treated Target Joint Bleed". Increases in the Pettersson score (a validated radiological scoring system that assesses the sum of joint damage in a patient) drove new arthropathy development (and transition between sub-models) and joint replacement surgery. The model was run with weekly cycle lengths.

c. SMA Type 1 – One aim of the original analysis was to evaluate the long-term cost-effectiveness of Zolgensma versus best supportive care in patients with Type 1 SMA. The model was dependent on three constructs: the motor function milestones achieved, need for permanent ventilation, and the time to death. The motor function milestones included sitting and walking. Other interim motor function milestones such as head control, rolling, crawling, and standing were not modelled as explicit health states, but health benefits associated with such improvements were included as a utility benefit with intervention. The model contained two main components: 1) a short-term model concordant with clinical study data, and 2) a long-term extrapolation model. Data inputs for the short-term model for each intervention were derived from their respective clinical trials and used directly to determine patient proportions in each health state at different time points in this model. The long-term model involved the extrapolation of motor function milestones, permanent ventilation status, and mortality rate, the latter of which was assumed to be conditional on health state, over a lifetime horizon using monthly cycles. In the base-case analysis, we assumed that the motor function milestones achieved at the end of follow-up in the clinical trials were sustained until death (i.e., patients stayed in the same motor function milestone-based health state until death).

II. Optimistic Scenario: These analyses will assume an increase in therapy effectiveness, generally in magnitude of effect during or beyond trial duration. Inputs and assumptions for these scenarios for each of the models are specified below.

a. B-cell Lymphoma – We will assume that all patients alive and responding to Yescarta at the end of the trial period (rather than after five years) will be considered cured. Health care costs, utilities, and mortality for the cured proportion will be defined as per the base case analysis.
b. Hemophilia A – With both the one-time and long-term hypothetical therapies, we will assume that 50% are cured, with those cured accruing any non-hemophilia treatment costs and QALYs as the hemophilia population in a health state where they don't experience any bleeds. We will assume that the remaining 50% accrue costs and QALYs as for the population treated with Hemlibra. This will include the assumed cost of the one-time gene therapy or long-term potential cure plus other non-drug health care costs.
c. SMA Type 1 – For patients treated with Zolgensma, we will assume a cure fraction that represents a 25% increase in the percentage of patients being able to walk as compared to the base case analysis, with this percentage contributed from those in the sitting health state. As in the base case model, this increase was assumed at the time point when the trial ended with patients remaining in the same health states for the remainder of the model duration unless they died.

III. Conservative Scenario: This scenario will assume a deteriorating effect during or beyond trial duration, based on modeled therapy. Inputs and assumptions for this scenario for each of the models are specified below.
a. B-cell Lymphoma – We will assume a 25% decrease in response rate in the Yescarta arm at the five-year time point compared to what was extrapolated in the base case analysis. We will accomplish this by modifying the extrapolation from the end of the trial period to the five-year time-point by fitting appropriate parametric curves to represent a 25% decrease in responders at five years.
b. Hemophilia A – With both the one-time and the long-term hypothetical therapies, we will assume that all patients had a 25% increase in bleed events compared to BPA prophylaxis, but still worse than that observed with Hemlibra in the base case analysis. This scenario will assume a 0% cure rate.
c. SMA – For patients treated with Zolgensma, we will assume a 50% drop in cure fraction 10 years after patients enter the model. This decrease in cure fraction will be assumed to occur exactly at the 10-year time point in the model, with no gradual decline. Thus, among those walking at the end of the trial period, 50% of these patients will transition to sitting health state and accrue costs and QALYs associated with this health state, without further deterioration through the remainder of the modeled time horizon.

2. Value-Based Pricing Criteria

Value-based price ranges for specific treatments will be calculated such that, for a derived price, at least 50% of probabilistic analysis simulation results produce incremental cost-effectiveness ratios that are at or below $150,000 per QALY and at least 90% of simulation runs producing incremental cost-effectiveness results at or under $250,000 per QALY. The

threshold of $250,000 per QALY was chosen to represent a value well-above the commonly cited threshold of $150,000 per QALY.

Discounting

Our literature review and comments from various stakeholders pointed out the impact of using various discount rates, as well as using differential rates for costs and outcomes. We will continue using the 3% discount rate for costs and outcomes in our base case analyses. In addition to this, we will include four discounting scenarios:

Table D1. Discounting Scenarios

Scenario	Discount Rate for Costs	Discount Rate for Outcomes
Base Case	3%	3%
Lower Rate	1.5%	1.5%
No Discounting	0%	0%
Differential	3%	1.5%

We are not exploring a scenario using hyperbolic discounting to reflect populations' varying consumption preferences over time, as this approach is considered more useful descriptively rather than prescriptively.

Additional Elements of Value

1. **Value of Hope**
2. **Insurance Value**

Magnitude of Health Gains and Cost Offsets

1. **Health care cost exclusion**

We will undertake an analysis where non-intervention treatment costs are excluded, so that the analysis includes only the intervention costs over the time horizon of the model. This analysis will be undertaken to highlight the impact of expensive therapy costs alone that contribute to the total costs and subsequent incremental cost-effectiveness results.

2. **Shared savings**

If cost offsets surpass $10 million, analyses will be conducted in which 50% of cost offsets will be captured by the intervention as part of its value-based price. We chose a value of $10 million to indicate the value of a human life which has earlier been estimated to range between $7.9 million and $9.1 million.

Model Outcomes

Model outcomes will include total LYs, QALYs, total costs, and incremental cost-effectiveness ratios for each model. All outcomes will be compared to those seen in our original analyses, with magnitude of difference in outcomes between those in the original analyses and those in the above defined modeling approaches quantified. Once all modifications are evaluated, we may run analyses with potential combinations of methods to determine their combined impacts on the estimated cost-effectiveness of treatments. All probabilistic analysis outcomes will be calculated over a minimum of 1,000 simulation runs.

Model Validation

We will use several approaches to validate the methods being tested in the models. First, we will have two internal reviewers validate results against methods adopted, with focus on checking for any unintended results for the methods used. Then we will provide preliminary proposed methods and results in our draft white paper. Based on feedback received, we will revise the methods and assumptions used in the models, as needed.