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# Uncertainty and Cures: Discontinuation, Irreversibility, and Outcomes-Based Payments: What Is Different About a One-Off Treatment?

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## ABSTRACT

Payers are concerned that one-off "cures" bring great uncertainty with the consequential risk of incorrect adoption decisions, and significant budget impact from large one-off payments. Innovators worry about bias against "cures" in favor of repeat treatment, which is not in patients' interests. We find that even in the absence of a difference in uncertainty of outcomes, adverse pay-offs differ. The greater financial risk associated with a cure is related to the issue of treatment discontinuation, driven by irreversibility. This paper uses a stylized example to illustrate the need to separate three different elements of the issue: (i) one-off versus repeat or ongoing treatment, (ii) duration of treatment effect, and (iii) the potential role of financial arrangements or risk sharing to mitigate the financial risk to the payer. It concludes that: (i) prevalence and discontinuation issues mean that the impact on the payer of an incorrect decision is greater with a one-off treatment than a repeat therapy; (ii) with evidence collection this risk diminishes over time (a form of CED or OWR); and (iii) financial arrangements or risk sharing can eliminate differences for the payer as between one-off and repeat therapy. The impact of (iii) also addresses payer concerns about budget impact.

*Keywords:* curative therapies, economic evaluation, treatment discontinuation, uncertainty.

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## Introduction

The advent of "cures" for gene disorders[1] and for some long-term conditions such as hepatitis C virus has raised several policy and analytical challenges. These arise in part from both assumptions routinely made when conducting cost-effectiveness analysis, which might need to be revised when evaluating cures, and rigidities within most healthcare systems, which are particularly acute when dealing with a cure. We assume that the healthcare system should not be biased in favor of cures, or biased against them. Cures should be judged in terms of the expected returns offered to the payer and the patient. Challenges that arise in assessing expected returns include the following:

1. One-off payments raising issues of "affordability." At any given cost-effectiveness or value threshold, a one-off treatment delivering a lot of health gain will likely have a much higher price per dose and, therefore, a larger budget impact than a repeat application treatment. We can think of this as a nonmarginal impact challenging the implicit assumption that cost-effectiveness analysis is conducted at the margin, an assumption that enables us to use a constant threshold incremental cost-effectiveness ratio (ICER). A number of options to tackle the affordability issue have been set out previously.[2,3] Nevertheless, there is evidence that payers are reluctant to increase budgets to accommodate higher prices, preferring to put pressure on innovators to negotiate.[4]
2. Although economists argue for a societal perspective to be taken when looking at costs and benefits, in reality, payers take a narrower perspective.[5] In the case of a cure, they can incur costs, but the long-term benefits accrue to, and hence move with, the patient. This is an issue in any system, including the United States, where patients have the ability to move plans but a reinsurance or risk adjustment mechanism is absent.[1,6]
3. The degree of uncertainty about the health gain associated with the treatment. Economic evaluations typically model over the period in which costs or outcomes could be assumed to be different to the comparator. Differences in the potential for discontinuation as between therapies are usually not factored in. In the case of a one-off cure this becomes an important factor.
4. Whether a cure "locks in" aspects of market dynamics to the detriment of the payer? There is a question as to how the market might develop in relation to competitive entry during both on-patent and off-patent periods. This could lead to changes in price and cost-effectiveness in a repeat application

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treatment. For example, exploitation of competitive market dynamics was crucial to payer management of the costs of direct-acting antivirals to tackle hepatitis C virus.[7]
5. The argument that cures should get a premium because of the positive effects for patients of knowing that they are going to be cured as opposed to being managed in a poorer health state. This benefit of knowing is taken to be additional to incremental health gains for the patient.
6. Whether a lower discount rate is appropriate for long-lived effects?

In this article, we use a stylized example to focus on challenges 3 and 4, although what we show also has implications for 1 and 2. We do not address challenges 5 and 6.

## Aspects of Uncertainty in Relation to Cures

For simplicity we focus on one uncertain parameter—duration of treatment effect. We assume that although the *existence* of the health effect is immediately visible, the *duration* of the health effect is unclear. The consequences of the effects not lasting may be either reversion to the previous health state (with whatever treatment regimen was supporting this) or a need to re-treat with the cure; that is, the effect is not permanent but can be repeated. For simplicity we assume reversion to the previous health state is the only option.

We consider whether the way in which uncertainty surrounding which option to select (ie, decision uncertainty) is handled should, or does, differ as between a cure that is delivered by a one-off treatment and a repeat-dose treatment (ie, an ongoing treatment that requires regular administration), but achieves the same expected health gain while treatment is continued. If mechanisms for handling decision uncertainty and its consequences in economic evaluations and in payer/health technology assessment body decision-making processes create a bias against a cure (eg, by requiring a much lower price for a cure as compared with a repeat treatment for an equivalent health effect), this would create inefficient incentives for research and development. If, however, the consequences of the decision uncertainty associated with a cure are different from those of an ongoing treatment, then we need to examine how this can be managed efficiently, so the appropriate differential incentives for research and development are sent.

## Managing Decision Uncertainty

There are 3 related aspects to the challenge of managing decision uncertainty and its consequences around cures.

The first is the effect of the one-off treatment as compared with the ongoing treatment. New adverse evidence (eg, the cure only lasts for 3 years) will have a different effect on the use of a one-off form of a curative therapy, as compared with the use of a repeat treatment. In both cases, new patients will not commence treatment. In the case of existing patients, the one-off treatment is irreversible and cannot be discontinued. This is not the case for a repeat treatment. This differential impact of new adverse evidence will also depend on the relative importance of prevalence and incidence, when the treatment first becomes available. The greater the ratio of prevalence to annual incidence, the greater the impact of irreversibility from a one-off cure as compared with an ongoing treatment. This effect will be compounded if the existence of the one-off cure leads to a large number of patients coming forward to seek the treatment, raising the observed prevalence of the disease.

The second is determining the value of collecting more information. There is likely to be sizable decision uncertainty. We assume that additional evidence can be collected by following patients over time, and that such a study is likely to be inexpensive compared with the expenditure on treatment. This is because only a subset of patients will need to be followed and evidence collection and analysis costs are likely to be small relative to treatment costs. Thus, adoption, if the treatment is expected to be cost-effective, without the collection of any further evidence is unlikely to be optimal given high decision uncertainty and the low costs of further research. Delaying adoption while waiting for long-term evidence has the challenge that patients who can be expected to benefit from the treatment will be denied access and the potential health losses are high. Coverage with evidence development (CED),[8] alternatively called adoption "only with research" (OWR),[9] appears likely to be optimal, although implementation of CED schemes is not straightforward.[10] This will require a study that can be undertaken while the drug is made available to all eligible patients (eg, using a single-arm trial or an observational study or even a randomized controlled trial undertaken in another health system where the drug is not available). A prospective observational study in which health status and mortality rates are analyzed each year for a cohort of patients is likely to minimize delay in identifying any issues with the cure. The irreversibility associated with one-off cure is likely to be large. If the results suggest that it is not expected to be cost-effective but there is value in collecting additional information, then this could likely be handled as "only in research" (OIR)[9] to avoid widespread adoption.

The third is the potential use of innovative payment mechanisms to manage the decision uncertainty for the payer given the nature of a one-off treatment and the irreversibility challenge to a CED/OWR/OIR solution. Risk-sharing arrangements have been reviewed[10] and proposed in the context of chimeric antigen receptor T-cell therapy, a new type of therapy that uses the patient's immune system to kill cancer cells.[11,12] In terms of the International Society for Pharmacoeconomics and Outcomes Research Performance-Based Risk-Sharing Task Force Report, an agreement could be of the "performance-linked reimbursement" form with rebates linked to the outcome achieved for each individual patient, or of the CED form in which a population sample is studied and the results generalized to the patient population. Various solutions have been put forward to avoid large one-off payments for the health gain expected with a cure.

Two forms of performance-linked reimbursement that are particularly relevant to handling the potential financial consequences of uncertainty are outcomes-related payment and amortization. Outcomes-based payments involve the payer making an annual payment to the innovator on the basis of the continued achievement of some outcomes; here, this would likely be based on the number of patients where the treatment is confirmed as still providing a cure. Regular (say annual) patient checkups are made to see whether the health gain expected from the treatment is still occurring. The innovator receives no further payments after a treatment failure from whatever cause. There are costs associated with outcomes-based schemes in terms of negotiation and in terms of evidence collection, although the costs of evidence collection may be the same as for a repeat-dose cure—for instance, where there is an annual health check of the patient to see whether the therapy is still working. Edlin et al[13] have used the term "technology leasing reimbursement scheme" to describe such a scheme. Amortization, in contrast, requires payers to meet a schedule of annual payments while the patient is alive irrespective of whether the therapy is still working. This has been proposed by Montazerhodjat et al[14] in the context of bringing in third parties to pay companies upfront and manage risk, collecting payments from the payers for as long as the patient survives.

Our starting point is that one, or both, of these approaches might be expected to equate the one-off cure with the repeat

**Table 1.** Parameters in the stylized example.

| Parameter | Current treatment | One-off cure | Repeat-dose cure |
|---|---|---|---|
| Prevalence | | 8000 patients | |
| Discount rate for costs | | 5% | |
| Discount rate for effects | | 5% | |
| Background mortality | | 0.05%/mo | |
| Disease mortality | 0.5%/mo | 0%/mo* | 0%/mo* |
| Utility | 0.0025 | 1* | 1* |
| Treatment cost | $740/mo | $296 741 | $4502/mo |
| Annual monitoring cost | NA | $120 | $120 |
| Probability of cure | 0% | 100%† | 100%† |

NA indicates not applicable.
*Only apply while treatment remains effective. Once treatment stops being effective, mortality and utility revert to values for current treatment.
†Probability of cure associated with both one-off and repeat-dose treatments is assumed to decline to 92% by 30 y.

treatment cure for the payer in that if new evidence indicates that the cure is no longer working, the payments stop, equivalent, in financial terms for the payer, to being able to discontinue a repeat-dose therapy. We assume that the evidence relates to effectiveness rather than to safety (in the form of adverse events), so it is equivalent for the patient. Nevertheless, adverse health effects may be irreversible in the case of the one-off cure as compared with the repeat-dose cure. We do not discuss this issue further, but clearly there is potentially greater risk in the use of advanced therapies. Financial adjustments can be made ex post, but harm to patients may be irreversible.

## A Stylized Example

We explore these 3 aspects of decision uncertainty with the use of a stylized example using 2 different alternative treatments, for the same condition, compared with current treatment. For this example, we assume that current treatment is relatively inexpensive compared with the new curative treatments, but also not particularly effective with no impact on mortality but some limited improvement in quality of life (see Table 1 for details). The 2 alternatives to current treatment that are being considered independently for development are a new ongoing treatment, which involves regular doses of therapy expected to cure the disease while the patient remains on treatment, and a new one-off treatment. This treatment is expected to cure the disease.

Both curative treatments are assumed to be 100% effective in the initial couple of years but the effectiveness is assumed to wane over time, reducing to 92% by year 30. Although effective, both curative treatments improve quality of life, generating an expected additional 5.49 quality-adjusted life-years (QALYs) over the 50-year lifetime of the model. Both curative treatments are also assumed to involve annual monitoring costs to determine whether the treatment is still effective. Both costs and outcomes are discounted at a rate of 5% per annum. The prices of each of the curative treatments are set to generate an ICER of $40 000/QALY compared with routine therapy; thus, both treatments would be considered cost-effective at an assumed threshold of $50 000/QALY.

We model the financial consequences for payers of different treatment outcomes under a one-off as compared with a repeat-dose cure. With the one-off treatment, it is possible to stop new patients receiving therapy but treatment costs for existing patients are irrecoverable. With the repeat-dose therapy it is possible to stop both new patients receiving treatment and treatment for existing patients. For simplicity, and to focus on the impact of the irreversibility between the 2 curative treatments, the example assumes that the treatments are used to treat the current prevalent population (of 8000 patients) but that there is no ongoing incident population. This maximizes the difference as between the one-off and repeat therapies in terms of the impact of new information on the potential for discontinuation.

We then model the impact of using 2 different payment mechanisms for the one-off cure. The first is an annual outcome-based "success" payment for each year for which the patient continues to benefit from treatment; that is, the patient is alive and treatment continues to work. This payment is set at $57 499/patient and is determined to generate a cost, over the expected lifetime of successful treatment, equivalent to paying for the one-off treatment upfront. The second is an annual annuity payment, based on amortization, in which payment is made only for patients who are alive. This is less sensitive to the treatment no longer working. The 2 approaches would be equivalent if treatment failure resulted in rapid death.

## Modeling Results

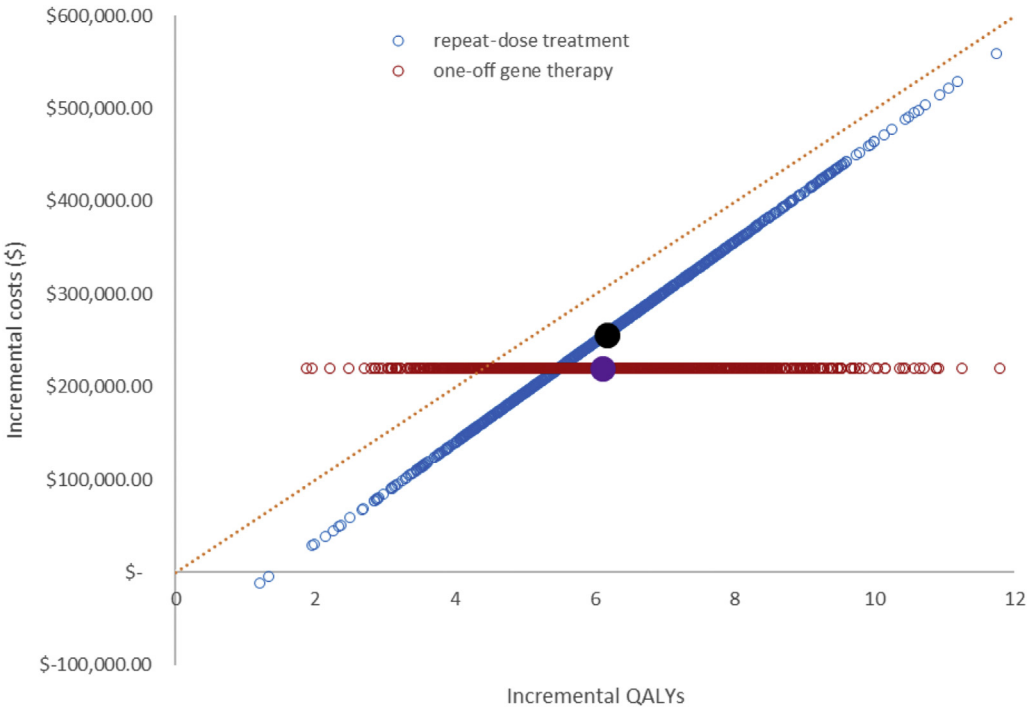
Figure 1 presents the incremental costs and effects associated with the one-off and repeat-dose treatments (compared with routine treatment) in the incremental cost-effectiveness plane. Given the fixed, upfront, cost associated with the one-off treatment, there is very little uncertainty in the associated expected costs (essentially a horizontal line) although there is considerable uncertainty in the expected QALYs associated with treatment. For the repeat-dose therapy, there is a high level of uncertainty in both the expected costs and expected QALYs and the 2 are positively correlated, reflecting the fact that the iterations where the treatment generates the most QALYs (ie, treatment is most effective) involve longer treatment duration and thus greater costs.

As such, for the one-off treatment it is the iterations in which the treatment is least effective (ie, the duration of effect is the shortest) that are not cost-effective whereas the opposite holds for the repeat-dose treatment. Here, it is the iterations in which the treatment is most effective (ie, the duration of effect is the longest) that result in ICER values that are close to (above) the threshold. This is because in these iterations the costs of repeat-dose treatment are higher, and because of the assumption of waning effectiveness, the additional cost of producing each additional QALY increases in these iterations.

Figure 2 shows the cost-effectiveness acceptability curve (CEAC) and the expected value of perfect information (EVPI) associated with the one-off treatment and repeat-dose treatment, respectively, compared with routine treatment. The degree of decision uncertainty (as measured by the EVPI) associated with the one-off treatment is 4 times that of the repeat-dose treatment, with a maximum population EVPI of more than $160 million as compared with less than $40 million, and a probability of being cost-effective at the $50 000 threshold of 86% as compared with 100% for the repeat-dose treatment. Because treatment outcomes are the same in terms of QALY gains and the net present value of treatment cost is the same, and we have only a prevalence effect with no continuing incidence, the only difference between the 2 treatment profiles is the discontinuation effect, that is, the irreversibility of payment should the one-off treatment stop working. The effect of introducing an outcomes-based payment equivalent to the cost of the one-off treatment will, however change the profile of the one-off treatment to resemble the ongoing treatment (ie, the *financial* irreversibility is removed for the payer).

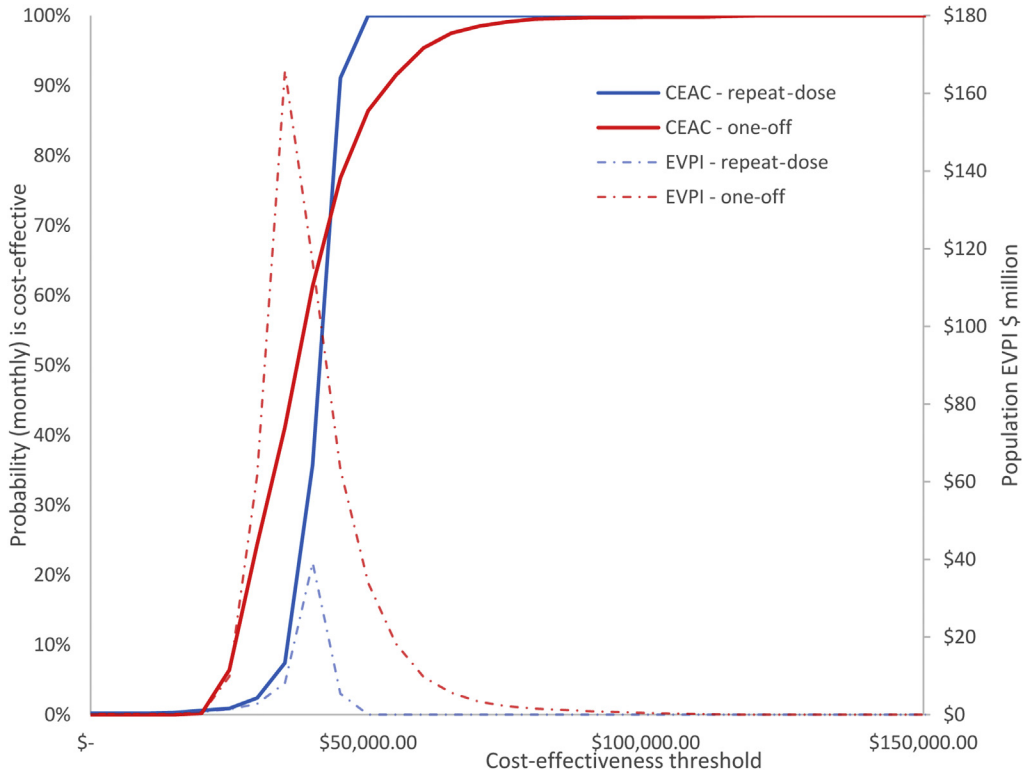
The results of using an outcomes-based payment versus an annuity payment can also be illustrated and compared with the annual cost of the repeat-dose treatment ($54 024/patient plus

**Figure 1.** Comparison of one-off treatment and repeat-dose treatment in the cost-effectiveness plane.



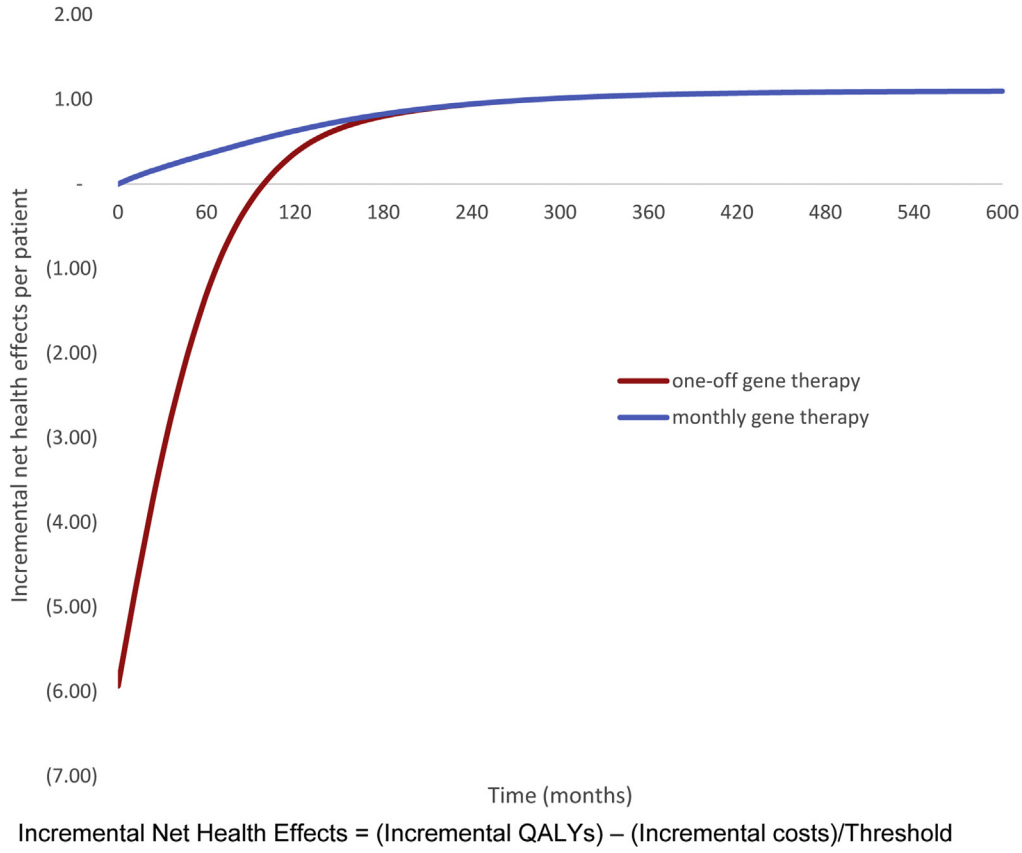

QALY indicates quality-adjusted life-year.

**Figure 2.** CEAC and EVPI for the one-off treatment and the repeat-dose treatment.




CEAC indicates cost-effectiveness acceptability curve (left-hand axis); EVPI, expected value of perfect information (right-hand axis).

**Figure 3.** Incremental NHE per patient for the one-off treatment and the repeat-dose treatment.




NHE indicates net health effects; QALY indicates quality-adjusted life-year.

annual monitoring cost). The annuity payment is $26 276/annum, paid for each patient, each year they remain alive, and the outcomes-based payment is $57 499/annum, paid for each patient, each year they remain cured.

The annuity payment is less than half of the outcomes-based payment, because although patients face higher death rates if the treatment stops working for them, many live for a number of years. The total number of life-years (undiscounted) in the model on which the annual payment is made is more than 160 000 (equivalent to 20.22/patient), but the number of "cured" life-years on which the outcomes-based payment is made is only just over 52 000 (equivalent to 6.51/patient). After discounting, the ratio of life-years to cured life-years falls from 3.10 to 1.80, equivalent to the ratio of the outcomes-based payment to the annuity payment seen here.

This indicates the need for caution in using surrogates for the outcome required. Although the costs associated with assessing whether the patient is alive/dead are lower than the costs of monitoring patient health status, this has to be set against the likelihood that payments may not match benefits. The greater the mortality rate from the disease, the closer the 2 sets of payments are likely to be. If the main benefit is a transformation of quality of life, then there is likely to be little relationship.

## Estimating Population Health Effects and Costs

Figure 3 sets out the net health effects (NHE) per patient over time for the 2 forms of treatment. The annual payment mechanism reduces the breakeven for the one-off treatment by making it equivalent to that for the repeat-dose treatment. Several authors have promoted the use of population and individual NHEs.[11,13] These are equivalent to net monetary benefits when the health gain is measured in QALYs and valued at the cost-effectiveness threshold. Edlin et al[13] use a "net benefit probability map" that shows the expected net health benefit measured in QALYs (and valued at an assumed cost-effectiveness threshold), that is, NHEs by another name. NHEs at an individual level show the point at which a therapy becomes NHE-positive—the breakeven point. If most expenditure is early, and most returns come later, as in our case, then this breakeven point comes some years after treatment commencement—about 7-8 years in our example. With population NHEs, the breakeven point will be even further delayed, as successive cohorts of patients begin treatment, thus delaying the breakeven point for the population treated by the payer. Over time the NHE associated with the 2 treatments converge because they are associated with equivalent ICER compared with routine therapy (ie, both have an ICER of $40 000/QALY).

The obvious question is what does this mean. Outside of healthcare, for a commercial investor, years to breakeven is not a meaningful concept in decision making. What matters is the expected return and the ability (or not) to manage uncertainty in a way that has an impact on the likely return, for example, by having options to discontinue investment should the expected return fall below an acceptable level. The same is, of course, true for a payer investing in a new drug. What matters is not time to breakeven but meeting the investment return criteria (ie, the cost-effectiveness threshold) and managing the consequences of uncertainty to the extent possible either through the collection of further information or through financial agreements, where either gives rise to options that can change expected returns.

**Table 2.** Impact of competition and patent expiry on expected payer costs.

| Year 0 cohort 8000 patients | 90% price reduction for the ongoing treatment because of generic/biosimilar entry in year 10 | | 50% price reduction for the ongoing treatment because of competitive entry in year 5, and 90% price reduction (from year 0 price) for the ongoing treatment because of generic/biosimilar entry in year 10 | |
|---|---|---|---|---|
| | ICER | Total payer costs (in million) | ICER | Total payer costs (in million) |
| One-off treatment | $40 000 | $2385 | $40 000 | $2385 |
| Repeat-dose treatment | $37 837 | $2290 | $31 496 | $2012 |
| Difference ($) | $2163 | $95 | $8504 | $373 |
| Difference (%) | 5.4% | 4.0% | 21.3% | 15.6% |

ICER indicates incremental cost-effectiveness ratio.

What such an NHE breakeven analysis may indicate is the size of the possible *irreversible* expenditure. This is relevant to a consideration of delaying investment to increase knowledge of expected returns, thus avoiding incurring the irreversible costs of adoption. Of course, not treating patients we expect to benefit is also irreversible, which has to be factored into the calculation. But again, what matters is not the possible size of any irreversibility, but whether it changes the value of options to collect evidence, delay adoption, or enter into financial agreements.

NHE per patient illustrates the initial investment by the payer if the one-off treatment is used, but it is not clear whether it adds anything to the ICER, CEAC, and EVPI illustration other than to make decision makers very aware of the size of uncertainty. Nevertheless, the key issue is expected value (for a risk-neutral payer) and the costs and benefits of investing in uncertainty reduction, that is, the consequences of uncertainty for decision making, not the uncertainty itself.

## The Challenge of a High-Cost/Low-Value Comparator

Pearson[15] has highlighted the challenge of an expensive cost-ineffective comparator. We can use our stylized example to illustrate the effect of having a high-cost/low-value comparator that is not cost-effective at a threshold of $50 000 and yet is used despite not offering good value for money.

We now assume that the current treatment is priced 10 times higher at $7400/month (rather than $740/month). In this case, the price to the payer associated with the one-off treatment or repeat-dose treatment can increase to over $1.0 million, an increase of more than $700 000, while maintaining an ICER of $40 000/QALY.

It could be argued that replacing expensive treatments that do not work very well offers bigger benefits over time, if not immediately, to the health system. This is the incentive that should be offered to innovators. Nevertheless, it could be argued that paying for health gain is different to paying for cost savings. On this basis one could argue, for example, that the cure should only get the incremental value over and above a cost-effective comparator, that is, at a price equivalent to $50 000/QALY. This would reduce the price of the comparator to about $8/month, to stay within the payers' ICER threshold of $50 000/QALY, and so reduce the price of the one-off curative therapy from more than $1.0 million to $218 000, lower than the initial price of $296 000. The revised price of $218 000 would then primarily reflect health gain, because comparator costs, when reduced to a cost-effective level, are small.

## Dynamic Market Conditions

We might expect reduced gains for the payer from the one-off treatment in respect of the entry of competing products during the on-patent period and the product going off-patent. This is because at launch the one-off treatment is priced (and assessed) taking account of the full expected health gains in the absence of competitive entry, as is normally the case when payers assess dossiers for the purposes of listing. Payers are less able to benefit from competition and patent expiry than with a repeat-dose treatment, where treatment switching for new and existing patients is feasible, enabling payers to introduce price pressure. To illustrate these effects, we compare the budget impact to the payer and effect on the ICER of

1. buying the one-off treatment as compared with the repeat-dose treatment, assuming no change in price throughout the period of treatment;
2. a patent expiry scenario in which prices for both the one-off treatment and the repeat-dose treatment fall by 90% after patent expiry, which we assume happens 10 years after the launch of the product;
3. a scenario in which, in addition to patent expiry, new entrants into the market after 5 years lead to a 50% fall in price for both the one-off treatment and the repeat-dose treatment.

In our example we only have an initial cohort, so there is no effect on the price of the one-off treatment. The effects on payer expenditure of a one-off treatment as compared with an ongoing treatment are presented in Table 2.

These differences are important and would be larger if there were cohorts of new (incident) patients each year. For example, for a new cohort starting in year 4 with competitive entry in year 5 and patent expiry in 6 years, the percentage differences in revenues between the one-off treatment and the repeat-dose treatment could exceed 50% of costs to payers. This could be dealt with by the payer and the innovator agreeing to adjust either the one-off payments or the outcomes-based payments in advance in expectation of competition or by building in price adjustments to the outcomes-based payments to be triggered by competitive entry.

## Discussion

Our results indicate that there can be real consequences for decision uncertainty for a one-off treatment as compared with an ongoing treatment that produces the same expected health effect.

These arise from the irreversibilities associated with one-off treatment because of the loss of options for treatment discontinuation.

Nevertheless, outcomes-based payments linked to additional evidence collection can produce financial equivalence between the one-off treatment and the ongoing treatment—resolving the irreversibility faced by the payer. In the event that additional evidence collection is not feasible, risk-neutral payers need to act on the basis of the expected ICER. If the innovator is unwilling to support the payer in a strategy of evidence collection, then the payer should look for a lower price to "buy out" the decision uncertainty that evidence could have resolved.

Other elements of our results indicate the following:

- There are substantial differences in the payment profiles associated with outcomes-based payments and annuity payments linked to life expectancy. This suggests the need to exercise caution when departing from monitoring outcomes linked to treatment.
- When the one-off treatment or the ongoing treatment replaces an expensive comparator that is not cost-effective, the value of the new treatment is artificially inflated. One way to tackle this would be to reduce the price of the comparator to a cost-effective level.
- The competitive dynamics of the pharmaceutical industry can work to the advantage of payers. There is a risk that price reductions are "frozen out" for a one-off treatment as compared with an ongoing treatment. Nevertheless, outcomes-based payments could be set up to adjust to reflect changes in prices arising from competitive entry.

We make a number of simplifying assumptions and it is helpful to explore the likely direction in which they may bias the comparison as between one-off and ongoing curative treatments:

- We assumed prevalence only, with no incidence. The higher the incidence rate at any given prevalence, the lower the gap as between the one-off and ongoing treatments. This is because the one-off treatment will also not be given to new patients. The impact of the irreversibilities associated with one-off treatments being given to the prevalent patients will become less important over time.
- We assumed that if the cure stopped working, it was not possible to re-treat with the cure. If it is possible, the effects should be neutral as between the one-off and repeat-dose treatments. What will have an impact is the time duration before the treatment is found to have stopped working. The shorter this period, the greater the differential impact. In the extreme when the treatment stopped working after 1 year, no further repeat-dose treatments would be given and the irreversibility is maximized.
- We assume a discount rate of 5% for health gains and for costs. Rates of 3.5%, 3%, and even 1.5% are now used in some health systems. Use of a lower discount rate would increase the relative size of the irreversibility, because the longer term effects will have a higher present value.
- We assume a given underlying parameter uncertainty of the treatment whether given as a one-off or an ongoing therapy. If that parameter uncertainty was higher (lower), the decision consequences of the irreversibility at a given ICER threshold would likely be higher (lower).

## Conclusions

Payers are concerned that one-off cures bring great uncertainty with the consequential risk of incorrect adoption decisions, and significant budget impact from large one-off payments. Innovators worry about bias against cures in favor of repeat treatment, which is not in patients' interest. At stake is the need to ensure that health systems are not biased in either direction: "for" or "against" one-off treatments. We find that even in the absence of a difference in uncertainty of outcomes, adverse payoffs differ. The greater financial risk associated with a cure is related to the issue of treatment discontinuation, driven by irreversibility. Financial arrangements or risk sharing can, however, eliminate differences for the payer as between one-off and repeat therapies by removing the financial impact of the irreversibility. Outcomes-based payments rather than amortization payments are likely to better reflect the underlying irreversibility, but can be equivalent when treatment failure results in rapid death. We also note that pragmatic adjustments may need to be made to take account of cost-ineffective comparators and of the potential impact of new entrants, which will change the price dynamics as between the one-off and repeat forms of treatment.

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