

Whose costs and benefits?

Whose costs and benefits? Why economic evaluations should simulate both prevalent and all future incident patient cohorts

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1 **Abstract**

2 **Background** Most health technology economic evaluations simulate only the
3 prevalent cohort, or the next incident cohort of patients. They therefore do not
4 capture all future patient-related benefits and costs.

5 **Objective** We show how to estimate and aggregate the ICERs for both currently
6 eligible (prevalent) and future (incident) patient cohorts, within the same model-based
7 analysis. We show why, and in what circumstances, the prevalent and incident
8 cohort ICERs are likely to differ.

9 **Methods** Algebraic expressions were developed to capture all components of the
10 ICER in hypothetical cohorts of all prevalent patients and future incident patients.
11 Numerical examples are used to illustrate the approach.

12 **Results** The ICER for the first (i.e. next) incident cohort is equivalent to the ICER for
13 all future incident cohorts only when the discount rates for costs and benefits are the
14 same; otherwise, when the discount rate for benefits is lower than for costs, the ICER
15 for all future incident cohorts is lower than the ICER for the first incident cohort.
16 Separate simulation of prevalent and incident patients treated for a hypothetical
17 progressive chronic disease shows widely different ICERs according to which patient
18 cohorts were included when the discount rates were equal.

19 **Conclusions** In many circumstances, both the prevalent cohort and all future
20 incident cohorts should be modelled. The need for this approach will depend on the
21 likely difference in the ICERs for prevalent and incident patients, the relative size of
22 the two types of cohort, and whether costs and benefits are discounted at equal
23 rates.

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1 **Key words:** cost-effectiveness analysis, ICER, decision modelling, chronic disease,
2 technology assessment.

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Introduction

6 It is increasingly recognised that to inform decision-making at a regional or national
7 level, incremental cost-effectiveness ratios (ICERs) need to be based on rigorously
8 informed decision model-based analyses which compare the incremental costs and
9 effects of all relevant comparators, and typically for the remainder of patients'
10 lifetimes.¹ Also, to be consistent with the fundamental tenets of cost-benefit analysis,
11 such models should enable the valuation of costs and benefits "in each year of the
12 project" (p.4), or for the whole of a health technology's life.²

13 The prevalence and incidence of a disease are fundamental concepts in
14 epidemiology. The prevalence is the number of cases in a population at a specified
15 point in time, and the incidence is the number of new cases arising in a given period
16 in a population.³ We apply the equivalent concepts of the prevalent cohort and future
17 incident cohorts to model-based cost-effectiveness analysis. We define the prevalent
18 cohort as those patients eligible for the new technology at the time the technology is
19 first introduced. Any given patient will be eligible from the time when the technology
20 is first clinically appropriate (e.g. just diagnosed with multiple sclerosis and eligible for
21 drug treatment, or when first eligible for a hip replacement) until the time when the
22 new technology is no longer appropriate (e.g. patient dies, or the disease has
23 reached such a severe state that the drug is no longer effective, or the patient is too
24 old to receive a hip replacement). Next, we define the incident cohort starting t years
25 in the future (i.e. t years after the date of a technology's introduction) as comprising
26 those patients who first become eligible for the new technology (e.g. diagnosed) t
27 years in the future.

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1 Cost-effectiveness studies generally model either only the first incident cohort
2 of patients or only the prevalent cohort. We argue first that model-based economic
3 evaluations of new treatments should model the costs and benefits of all patients in
4 the prevalent cohort and in *all* future incident cohorts over the life of the technology.
5 We further recommend that overall cost-effectiveness should be based on all these
6 cohorts combined, i.e. that the ICER be calculated from a weighted sum of all these
7 costs and benefits.

8 The current ISPOR guidance on good practice in decision analytic modelling
9 focuses mainly on the structure of the model, the validation of the model
10 estimates/inputs, and the choice between alternative simulation models (e.g. Monte
11 Carlo vs. cohort).⁴ However, aside from some general encouragement to stratify
12 models by patient sub-groups, there is no specific advice on what starting
13 populations should go into a decision model. Nor does methods guidance from
14 national health technology assessment agencies state what current and future
15 populations of patients should be included in model-based analyses, e.g. UK,⁵
16 Australia,⁶ New Zealand,⁷ Canada,⁸ Germany.⁹

17 In this paper, we describe the mathematics for estimating the ICER that
18 includes the costs and benefits for both the prevalent and all future incident cohorts.
19 For simplicity, we consider a new technology versus a single comparator technology,
20 but the ‘comparator technology’ could represent no treatment. Equivalent equations
21 for more than two comparators in a net monetary benefit framework are given in the
22 Online Appendix. The technologies can be either a drug, a medical device, or a
23 screening program. We suggest parameters related to the structure of the patient
24 cohorts that could be included in the probabilistic sensitivity analysis.

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1 ICER for incident cohorts

2 First future incident cohort

3 Consider a cost-effectiveness model where future costs and benefits are modelled at
4 discrete times (e.g. a Markov model). Suppose the incremental costs, per patient
5 starting treatment, between the new and comparator technology (where the
6 comparator technology could be no technology, i.e. best supportive care), in cycles 0,
7 1, 2, ..., H are $\Delta K_0, \Delta K_1, \Delta K_2, \dots, \Delta K_H$ and incremental benefits $\Delta B_0, \Delta B_1, \Delta B_2, \dots,$
8 ΔB_H (Table 1). The time horizon is H cycles. For clarity, given that the ΔK_j and ΔB_j
9 are expressed per patient starting treatment, these quantities tend to zero with cycle
10 j , as patients die. Then the ICER as currently calculated for health technology
11 assessments for the first future incident cohort, given discount rate for costs of r^*_C
12 and benefits r^*_B over a cycle;

13

$$14 \quad \text{ICER (first future incident cohort)} = \frac{\sum_{j=0}^H v^*_C j \Delta K_j}{\sum_{j=0}^H v^*_B j \Delta B_j}$$

15

16 where we define $v^*_C = \frac{1}{1+r^*_C}$, $v^*_B = \frac{1}{1+r^*_B}$.

17

18 All future incident cohorts

19 Now assume, more realistically, that a new cohort of patients will become *eligible* for
20 treatment with the new or comparator technologies at the start of each of T years in
21 the future. The new and comparator technologies are assumed to become obsolete
22 after T years, possibly replaced by another technology. In this paper, we present all
23 analyses with closed-form algebra to aid understanding of the methods. However, it
24 is of course possible to simulate each future incident cohort. In general, assume that

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1 the number of eligible patients at the start of each cohort, relative to the number of
2 eligible patients at the start of the first year, is given by n_t at year t , so that $n_0 = 1$.
3 The n_t are commonly used in budget impact analyses. The n_t could increase with
4 year t , for example to model increasing numbers of Type 2 diabetes patients in the
5 future as obesity becomes more common. Assume further that the probability that an
6 eligible patient is given the new technology in the t^{th} year in the future is p_t . The p_t
7 could be described as the “rate of adoption”, “rate of uptake” or “market penetration”
8 of the new technology, and are also commonly used in budget impact analyses. The
9 graph of the volume of sales of a drug, i.e. the product $n_t p_t$, against year t is
10 generally \cap -shaped.¹⁰ The annual volume of a drug sold typically increases in the
11 first decade after drug launch, reflecting the diffusion of the new drug after launch.
12 The annual volume of a drug sold in the second decade after launch reflects post-
13 patent experience and declines as patients switch to newer drugs.^{10;11} Then, the
14 relative number of patients in the incident cohort starting t years in the future affected
15 by the new technology is $n_t p_t$. By analogy with the special case of two future incident
16 cohorts (see Online Appendix);

17

$$18 \quad \text{ICER (all incident cohorts)} = \frac{\sum_{t=0}^T n_t p_t v_C^{-t}}{\sum_{t=0}^T n_t p_t v_B^{-t}} \text{ ICER (first incident cohort)} \quad (\text{Equation 1})$$

19

20 where $v_C = \frac{1}{1+r_C}$ and $v_B = \frac{1}{1+r_B}$, and r_C and r_B are the “inter-generation” annual
21 discount rates for costs and benefits between the current time and the time of the
22 future incident cohorts. By contrast, r_C^* and r_B^* are the (per cycle) “intra-generation”
23 discount rates. We further assume that undiscounted incremental costs and benefits
24 are the same for all incident cohorts.

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1 From Equation 1, the ICERs for all future incident cohorts combined and for
2 the first future incident cohort are equal if the cost and benefit discount rates, r_C and
3 r_B , are equal. Alternatively, if $r_C > r_B$, the ICER for all incident cohorts is lower (see
4 Online Appendix). For example, in the Netherlands, where costs are discounted at
5 4% and benefits at 1.5% per year,¹² under certain assumptions, the ICER for all
6 future incident cohorts combined may be about ¾ of the ICER assuming a single
7 incident cohort (i.e. as calculated in the traditional way) (see Online Appendix).

8

9 When $n_t p_t$ is equal for all t , Equation 1 simplifies to;

10

11
$$\text{ICER (all incident cohorts)} = \left(\frac{1 - v_B}{1 - v_C} \right) \left(\frac{1 - v_C^{T+1}}{1 - v_B^{T+1}} \right) \text{ICER (first incident cohort)}$$

12

(Equation 2)

13

14 Now, if we assume that $n_t p_t$ follows a \cap -shaped quadratic curve, as is often the
15 case with drug sales volumes,¹⁰ then Equation 2 is applicable again (see online
16 Appendix). If independent estimates of $n_t p_t$ are available then they should be used in
17 Equation 1, otherwise Equation 2 is appropriate. Equation 2 is convenient since we
18 need only have an estimate for the single parameter T , not the $n_t p_t$ for all t .

19

20

21 **ICER for prevalent cohort**

22 In addition to the patients who will become eligible for the new technology in the
23 future, there may be patients who are already eligible at the time the technology is
24 introduced. Such prevalent patients would switch from the current to the new
25 technology. Denoting the incremental costs and benefits of the prevalent cohort at

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- 1 cycle $j = 0 \dots H$, expressed per patient at the start of the prevalent cohort, by ΔC_j , and
- 2 ΔQ_j , the ICER for the prevalent cohort is;
- 3

$$4 \quad \frac{\sum_{j=0}^H v^* c^j \Delta C_j}{\sum_{j=0}^H v^* B^j \Delta Q_j} \quad (\text{Equation 3})$$

5

6

7 **ICER for incident and prevalent cohorts combined**

- 8 We define N as the number of patients in the prevalent cohort that are eligible for
- 9 treatment, relative to the number of patients in the first future incident cohort, and \bar{p}
- 10 as the probability that a patient in the eligible prevalent cohort is given the new
- 11 technology, assumed constant over cycle j . Then in the general case of any number
- 12 of treatments, the optimal strategy is to choose the treatment with the maximum
- 13 expected net benefit¹³ (see Online Appendix). Returning to the particular case of two
- 14 treatments alternatives, we calculate the ICER as a “ratio of means”, in the
- 15 terminology of Stinnett & Paltiel (1997).¹⁴ In particular, the ICER equals total
- 16 incremental costs divided by total incremental benefits during the whole time the
- 17 technology is used:

18

19 ICER (prevalent and all future incident cohorts) =

20

$$21 \quad \frac{\bar{p}N \sum_{j=0}^H v^* c^j \Delta C_j + \left(\sum_{t=0}^T n_t p_t v_c^t \right) \left(\sum_{j=0}^H v^* c^j \Delta K_j \right)}{\bar{p}N \sum_{j=0}^H v^* B^j \Delta Q_j + \left(\sum_{t=0}^T n_t p_t v_B^t \right) \left(\sum_{j=0}^H v^* B^j \Delta B_j \right)} \quad (\text{Equation 4})$$

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1 In this equation we make the simplifying assumption that the proportion of patients in
2 a given incident cohort that are given the new technology, p_t , does not change over
3 cycle j . Note that if the cost and benefit discount rates are equal, then Equation 4
4 implies that the ICER for the prevalent and incident cohorts combined will lie between
5 the ICER for the prevalent cohort alone and the ICER for the first future incident
6 cohort alone.

7 We now introduce parameters to allow us to estimate N and \bar{p} . Denote the
8 average age of patients at the start of any incident cohort as A (assumed constant
9 over time). Suppose a patient is *eligible* for treatment with the new technology over
10 an average period of M years, from age A to age $A+M$. To avoid confusion, note that
11 parameter M relates to the age range of any given *patient*. It should not be confused
12 with parameter T , which relates to the age (lifetime) of the *technology*. Costs directly
13 associated with the technology occur during some, but not all the period of eligibility.
14 For example, for patients in the incident cohort, the cost of a hip replacement occurs
15 at the very start of the period of eligibility, whereas, the cost of a drug for a chronic
16 condition might occur over the whole period of eligibility, M .

17 When M is small, e.g. treatments for acute infection, the costs and benefits of
18 the incident and prevalent cohorts are similar, because the patients' initial
19 parameters, such as the average age and average severity of condition are similar
20 between the incident and prevalent cohorts (see below). Conversely, when M is
21 large, for example, for long-term therapies for chronic conditions, the costs and
22 benefits of the incident and prevalent cohorts can be substantially different for a
23 variety of reasons. Hence the ICER for the prevalent cohort is similar to the ICER for
24 the incident cohort for acute conditions, but can be very different for chronic
25 conditions. On average, we would expect that patients in the prevalent cohort will be
26 approximately half way through their treatment with the comparator technology.
27 Correspondingly, we expect that patients at the start of an incident cohort (i.e. at the

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1 start of their treatment) to be treated for approximately twice the length of time as
2 patients in the prevalent cohort.

3 If the number of patients in the prevalent cohort that are eligible for treatment,
4 relative to the number of patients in the first future incident cohort, N , is known from
5 the literature, then this value should be used. For example, the annual incidence of
6 end-stage renal disease in the UK in 2003 was 5,517 patients, and the prevalence
7 was 34,259,¹⁵ which gives $N = 34,259 / 5,517 = 6.2$. Alternatively, we now describe
8 how to estimate N . Denote the probability that a patient who is treated with the
9 *comparator* technology survives from age A , at the start of an incident cohort, to age
10 $A + t$ as $s(A, A + t)$. Such data are often available from cost-effectiveness models.

11 Then;

12

13
$$N = n_{-1}s(A, A + 1) + n_{-2}s(A, A + 2) + n_{-3}s(A, A + 3) + \dots + n_{-M+1}s(A, A + M - 1)$$

14 (Equation 5)

15

16 Hence when M is large, for conditions that require a long period of treatment, N is
17 large, and when M is small, for conditions that require short-term treatment, for
18 example acute infection, N is small.

19 We estimate \bar{p} as the weighted average of the p_t , with the weights equal to
20 the number of patients in the prevalent cohort t years in the future;

21

22
$$\bar{p} = \frac{\sum_{t=0}^{M-1} \sum_{i=0}^{M-1} p_t n_{-i} s(A, A + t + i)}{\sum_{t=0}^{M-1} \sum_{i=0}^{M-1} n_{-i} s(A, A + t + i)}$$
 (Equation 6)

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- 1 where subscript $-i$ refers to the incident cohort that started i years in the past. Now
- 2 suppose the cost and benefit discount rates are equal, i.e. $v_C = v_B = v$. Then
- 3 Equation 4 becomes;
- 4
- 5 ICER (prevalent and all future incident cohorts) =
- 6

$$\frac{\frac{\bar{p}N}{\left(\sum_{t=0}^T n_t p_t v^t\right)} \sum_{j=0}^H v^{*j} \Delta C_j + \left(\sum_{j=0}^H v^{*j} \Delta K_j\right)}{\frac{\bar{p}N}{\left(\sum_{t=0}^T n_t p_t v^t\right)} \sum_{j=0}^H v^{*j} \Delta Q_j + \left(\sum_{j=0}^H v^{*j} \Delta B_j\right)}$$

- 7
- 8
- 9 From which it is clear that the prevalent cohort is negligible when $\frac{\bar{p}N}{\left(\sum_{t=0}^T n_t p_t v^t\right)}$ is
- 10 small. This is true when T is very large, or M is very small. We now consider three
- 11 cases;
- 12

- 13 1: Parameters for both the incident and prevalent cohorts are known
- 14 2: Parameters for incident cohort only are known
- 15 3: Parameters for prevalent cohort only are known
- 16
- 17

18 **Case 1: Parameters for incident and prevalent cohorts known**

- 19 Suppose we know the model parameters for both the incident and prevalent cohorts
- 20 from literature reviews of primary research. Then we can calculate ΔC_j , ΔQ_j , ΔK_j , and
- 21 ΔB_j . We then calculate the ICER for the incident and prevalent cohorts combined
- 22 from Equation 4, using an estimate of the p_t and hence \bar{p} (as explained in the

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1 Discussion). To calculate the ΔC_j , ΔQ_j , ΔK_j , and ΔB_j directly, we would need data
2 from two types of clinical trial. One trial (or trial subgroup) with patients from an
3 incident cohort, i.e. newly diagnosed, and another trial with patients from the
4 prevalent cohort. This would be especially useful if patients respond differently to a
5 new technology according to previous treatments received, for example, for
6 corticosteroids for asthma.¹⁶

7 If the prevalent cohort is large relative to the incident cohort, the range of
8 values of input parameters, such as patient age and disease severity, for patients in
9 the prevalent cohort may be wide. In this case, it may be preferable to allow for such
10 heterogeneity of input parameters in the cost-effectiveness model which is used to
11 generate the ΔC_j and ΔQ_j for the prevalent cohort. For example, the model could be
12 run for each of a range of patient ages, and the ΔC_j and ΔQ_j estimated as a weighted
13 average of the incremental costs and benefits for each model run, with weightings
14 proportional to the probability density function of each age (e.g. as in Dewilde &
15 Anderson 2004).¹⁷

16

17

18 **Case 2: Parameters for incident cohort only known**

19 Suppose we know the parameter values for the incident cohort only, e.g. if the clinical
20 trial(s) were based on incident cohorts of patients only. We now outline a method for
21 estimating the incremental costs and benefits for the prevalent cohort, ΔC_j , ΔQ_j . As
22 above, we then calculate the ICER for the incident and prevalent cohorts combined
23 from Equation 4. In the Online Appendix, we describe an alternative method for
24 estimating ΔC_j and ΔQ_j , where we estimate the parameter values that specify the
25 characteristics of patients at the start of the prevalent cohort. Although this second
26 method is simpler to implement than the first method, it is slightly less accurate
27 because we assume no variability in the input parameters of the prevalent cohort.

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1 Returning to the first method, suppose the costs in the incident cohort,
2 expressed per patient at the start of the incident cohort, are K_j and K'_j at cycle $j =$
3 $0 \dots H$ for the new and comparator technologies respectively (Fig. 1). As above, we
4 assume that these costs are the same across all incident cohorts. We cannot simply
5 assume that the future costs with the new technology for the incident cohort that
6 started in year t (i.e. in the past, so that t is negative), $K_{t,j}$, j cycles since the start of
7 the incident cohort, are given by K_j , because this would assume (incorrectly) that
8 patients had been treated with the new technology in the past. Instead, in the Online
9 Appendix, we show how to estimate the $K_{t,j}$ by an algorithm, which can be coded as
10 a macro. The prevalent cohort costs and benefits for the new technology at cycle $j =$
11 $0 \dots H$ are calculated as $C_j = \sum_{t=-(M-1)}^{-1} K_{t,j-t} n_t / N$ and $Q_j = \sum_{t=-(M-1)}^{-1} Q_{t,j-t} n_t / N$ and for the
12 comparator technology as $C'_j = \sum_{t=-(M-1)}^{-1} K'_{j-t} n_t / N$ and $Q'_j = \sum_{t=-(M-1)}^{-1} Q'_{j-t} n_t / N$ (Fig. 1).

13
14
15 **Case 3: Parameters for prevalent cohort only known**
16 In the Online Appendix, we describe a method to estimate the incremental costs and
17 benefits for the incident cohort, ΔK_j , ΔB_j , given that we know the parameter values,
18 e.g. average age, for the prevalent cohort only. As above, once we estimate ΔK_j , ΔB_j ,
19 we calculate the ICER for the incident and prevalent cohorts combined from Equation
20 4.

21
22
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24 **Example of application**

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1 Here, we apply the methods described above to an example cost-effectiveness
2 model of a new maintenance drug versus an existing comparator drug to treat a
3 chronic progressive condition. Details of the model structure and results are given in
4 the Online Appendix, however we provide a brief description here. We assume that
5 the new drug will be used in the health system for the next $T = 30$ years, and that the
6 probability that a patient eligible for treatment takes the new drug at time t , p_t , follows
7 a \cap -shaped quadratic curve. The relative number of patients in the incident cohort,
8 n_t , is assumed equal over time t . The new drug reduces the rate of disease
9 progression. Non-drug costs increase and utilities decrease with increasing disease
10 severity. The average age at diagnosis, i.e. at the start of an incident cohort, $A = 30$
11 years, and we assume a certain distribution across disease severity states for
12 patients in the incident cohort. Patients were modelled from age 30 to death or age
13 100. This gives $M = 70$ years over which patients are eligible to be treated with the
14 new drug.

15 We estimate that the prevalent cohort is $N = 47$ times the size of a single
16 incident cohort (Equation 5), and the average age of patients in the prevalent cohort
17 is approx. 56 years, compared to $A = 30$ years in the incident cohort. As expected,
18 patients are at a more advanced stage of illness in the prevalent cohort compared to
19 the incident cohort. The ICER for the first incident cohort was calculated as £25,000
20 per quality-adjusted life year (QALY). Given that the cost and benefit discount rates
21 were assumed equal, the ICER for all future incident cohorts combined was also
22 £25,000 / QALY. The total discounted costs and benefits for the prevalent cohort
23 were calculated using the algorithm described in the Online Appendix (Fig. 2). The
24 ICER for the prevalent cohort alone was substantially higher, at £94,000 / QALY, and
25 for both the prevalent and all incident cohorts combined, £57,000 / QALY.

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2 Discussion

3 In this paper we have argued that the cost-effectiveness of a treatment should be
4 assessed in relation to all patients whose costs and benefits will be affected; both
5 those currently eligible and those who will become eligible for the new treatment in
6 the future. On average, patients in the prevalent cohort will be older and will typically
7 be at a more advanced stage of disease than patients in the incident cohort.

8 Furthermore, the more life-years over which the technology is applicable for patients
9 (e.g. maintenance therapies for chronic conditions), the greater these differences. In
10 summary, the suggestions in this paper are particularly important to implement in
11 cost-effectiveness analysis in any of the following circumstances:

12

- 13 • for long-term therapies for chronic conditions (particularly for chronic progressive
14 conditions), e.g. Alzheimer's disease, multiple sclerosis, cystic fibrosis, diabetes,
15 eczema, rheumatoid arthritis.
- 16 • when the discount rates for costs and benefits differ.

17

18 In these cases, the ICER as calculated in this paper for all affected patients may
19 differ substantially from the ICER as traditionally calculated (for the next incident
20 cohort). In particular, we have described a simplified but realistic example cost-
21 effectiveness analysis of a chronic progressive condition, assuming equal cost and
22 benefit discount rates. In this example, the ICER as calculated by our method is 2.3
23 times the ICER as traditionally calculated by assuming just a single incident cohort,
24 and 0.6 times the other traditional method of assuming a single prevalent cohort.

25 We have shown that when the discount rates for costs and benefits differ, it is
26 particularly important to estimate the costs and effectiveness of all future incident
27 cohorts. While many health economists,¹⁸ and most country's official guidance for

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1 the cost-benefit analysis of health technologies,¹² recommend equal discount rates
2 for costs and benefits the matter is by no means settled. Some suggest r_C should be
3 greater than r_B .¹⁸⁻²⁰ In particular, Brouwer et al (2005)¹⁹ recommend $r_C = 3.5\%$ and r_B
4 = 1.5%, and Gravelle & Smith (2001)¹⁸ suggest that r_C should be 2-5% greater than
5 r_B . There remain some countries where different discount rates are recommended
6 for health care economic evaluations (e.g. Netherlands: $r_C = 4\%$, $r_B = 1.5\%$; and
7 Belgium: $r_C = 3\%$, $r_B = 1.5\%$; source, ISPOR website¹²).

8 An obvious question is: when the prevalent cohort is not negligible, when is
9 the ICER for the prevalent cohort greater than the ICER for the first future incident
10 cohort, and vice versa? We suggest an answer to this question for three types of
11 conditions-with-treatments. First, we have shown that for the example cost-
12 effectiveness model of a continuous treatment for a *progressive* chronic disease, the
13 prevalent cohort ICER is substantially greater than the incident cohort ICER, because
14 at each cycle, the ratio of incremental costs to incremental benefits is greater for the
15 prevalent cohort (Fig. 2 online Appendix). This may be a typical result for a
16 progressive chronic condition, supported by economic evaluations in cardiology.²¹
17 Nevertheless, this question warrants further analysis, particularly since a contrary
18 result has been found in a cost-effectiveness study of a cholesterol-lowering statin.²²
19 In this study, the incremental cost per life year gained was lower for older patients
20 than for younger patients. The difference in the ICERs was due to higher
21 incremental costs in the younger age group, but similar incremental life years gained.
22 Whilst these two patient groups did not correspond to incident and prevalent cohorts,
23 this result does suggest that the prevalent cohort ICER may, in some cases, be lower
24 than the incident ICER, given that patients in the prevalent cohort are, on average,
25 older than those in the incident cohort.

26 Second, we consider a continuous treatment for a non-progressive chronic
27 condition, such as asthma. Suppose there are two health states A and B, and
28 patients are in the worse state A (e.g. poorly controlled asthma) under the

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1 comparator drug and the better state B under the new drug. Suppose further that life
2 expectancy is independent of the drug and that costs are a function just of the drug
3 (higher for the new drug) and whether the patient is in state A (higher) or state B
4 (lower). Further, suppose that patient utility is a function of just the state, and is
5 higher in state B than in state A. In this case, the ratios of incremental costs and
6 benefits $\frac{\Delta K_j}{\Delta B_j}$ and $\frac{\Delta C_j}{\Delta Q_j}$ are constant over cycle j and are the same for the incident
7 and prevalent cohorts. Hence the prevalent cohort ICER equals the incident cohort
8 ICER.

9 Third, consider the scenario where the majority of costs are incurred up front
10 for chronic conditions. This is particularly appropriate for medical devices, such as
11 cardiac pacemakers for heart conditions and cochlear implants for deafness. Again,
12 suppose there are two health states A and B, and suppose that patients are in the
13 worse state A under the comparator technology and in the better state B under the
14 new technology. Again, suppose that life expectancy is independent of the
15 technology. Suppose the cost of the technology, e.g. cost of cochlear implant itself
16 plus cost of implantation surgery, is incurred in the first cycle, and is greater for the
17 new than the old technology. Health state costs can be higher or lower in state A
18 than in state B. Patient utility is again solely a determined by health state. In this
19 case, for the incident and prevalent cohorts, the ratios of incremental costs and
20 benefits $\frac{\Delta K_j}{\Delta B_j}$ and $\frac{\Delta C_j}{\Delta Q_j}$ are high in the first cycle, and far smaller in all future cycles.
21 The ratios for the two cohorts are equal by cycle. However, given that patients are
22 older in the prevalent than in the incident cohort, and will therefore use the
23 technology for fewer years, in the prevalent cohort, there will be fewer cycles with low
24 incremental cost/benefit ratios. Hence, the prevalent cohort ICER will be greater
25 than the incident cohort ICER.

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1 Another question is whether the ICER calculated according to our approach
2 will be greater or smaller than the ICER as traditionally calculated. In general, it is
3 not possible to say: some technologies will appear more cost-effective, and others
4 less cost-effective. Consider first the case when the prevalent cohort is negligible
5 compared to the incident cohort, for example with treatments for acute conditions.
6 Then, if the cost and benefit discount rates are equal, the ICER will not change.
7 Alternatively, if the discount rate for costs is greater than the rate for benefits, the
8 ICER will be less than traditionally calculated. Now, assume that the prevalent
9 cohort is not negligible. In previous model-based cost-effectiveness analyses, either;
10
11 1: all patient-related parameters (e.g. average age, average disability level) refer
12 to the prevalent cohort, or
13 2: all patient-related parameters refer to the incident cohort, or
14 3: some parameters refer to the prevalent cohort and the rest to the incident
15 cohort.
16
17 Again, assuming equal discount rates, in the expected scenario that the prevalent
18 cohort ICER is greater than the incident cohort ICER, the combined ICER as
19 calculated here would be lower than the ICER calculated in case 1, greater than in
20 case 2, and uncertain in case 3. Conversely, in the less likely event that the
21 prevalent cohort ICER is lower than the incident cohort ICER, then these conclusions
22 are reversed. However, in a review of model-based cost-effectiveness analyses, we
23 found very few studies that explicitly state whether model parameters were derived
24 from incident or prevalent cohorts. Therefore, our analysis suggests that the ICER
25 as calculated in previous cost-effectiveness analyses may be substantially different
26 from the ICER as calculated according to the methods of this paper. As a side issue,
27 note that we have assumed that the costs and benefits in all future incident cohorts
28 are equal. This assumption would be violated if, for example, one component of the

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1 costs is predicted to increase in the future at a different rate to the other components
2 of the costs. Then we must adjust Equations 1, 2 and 4 appropriately.

3 One disadvantage of our suggested methods is that they require estimation of
4 additional model parameters. The following algorithm may allow the analyst to
5 decide when it is necessary to implement our suggested methods. First, if the cost
6 and benefit discount rates differ, our suggested method should be followed.

7 Specifically, we must estimate the *relative* sizes of the affected patient populations
8 ($n_t p_t$) for each year in the future up to year $t = T$ (Equation 1). If such data is not
9 available, we suggest above that $n_t p_t$ can be assumed a quadratic function of year t .

10 We then require only an estimate of the lifetime of the new technology, T (Equation
11 2). Variability in $n_t p_t$ and/or T should be incorporated in the probabilistic sensitivity
12 analysis. The values of $n_t p_t$, T , and the variability in these quantities could be
13 estimated by analysing trends in the volumes of sales of similar technologies in the
14 past.

15 Next, what if the cost and benefit discount rates are equal? When the size of
16 the prevalent cohort is negligible compared to the size of the incident cohort, then the
17 ICER for the prevalent cohort and all future incident cohorts combined can be
18 approximated by the ICER for the first future incident cohort alone. However, when
19 the prevalent cohort is not small, the analyst should first compare the ICERs for the
20 prevalent and incident cohorts. Given that the ICER for both types of cohort
21 combined lies between the ICER for the prevalent cohort and the ICER for the first
22 future incident cohort when the cost and benefit discount rates are equal (see
23 analysis), if the two ICERs are similar, then the ICER for the prevalent cohort and all
24 future incident cohorts combined can be approximated by the ICER for either the
25 prevalent cohort or the ICER for the first future incident cohort. If the ICERs for the
26 prevalent cohort and first future incident cohort are not similar, then our method for
27 calculating a combined ICER should be used.

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1 The proposed method requires estimates of n_t and p_t separately for each year
2 in the future up to year $t = T$ in order to estimate \bar{p} (Equation 6). However, without
3 relevant data, it is reasonable to assume that the n_t are equal for all t . The p_t are
4 then estimated as described in the estimation of $n_t p_t$ above. Next, we must estimate
5 the size of the prevalent cohort relative to the size of the first future incident cohort,
6 N , and patient-related parameters, such as the average age and average disability
7 status for both the incident and prevalent cohort. Uncertainty in N should also be
8 reflected in the probabilistic sensitivity analysis. Given that the ICER can be greatly
9 altered by use of our proposed methods, the extra effort in estimating these
10 parameters and in adjusting the cost-effectiveness analysis is justified. Nonetheless,
11 we are mindful of the extra analytical effort and data requirements that are implied by
12 our methods. We have therefore also provided some practical tools for estimating
13 the costs and benefits for incident or prevalent patient cohorts when full data on the
14 other type of cohort is unavailable. Ideally, however, cost-effectiveness analyses in
15 these situations should be grounded in rigorous empirical studies which yield
16 separate effectiveness estimates and other data from both incident, newly eligible,
17 patients and those prevalent patients who are switching to the new treatment.

18 Given that the clinical and cost-effectiveness of a health technology can differ
19 by patient subgroup, national guidance recommends assessing cost-effectiveness
20 separately by patient subgroup (England,⁵ Australia,⁶ New Zealand,⁷ Canada,⁸
21 Germany⁹). The characteristics of patients in the subgroup should be identified on
22 the basis of an *a priori* expectation of differential clinical or cost effectiveness due to
23 known, biologically plausible mechanisms, social characteristics or other clearly
24 justified factors.⁵ Disease severity is an example of such an *a priori* factor. For
25 example, consider a chronic progressive disease, with cost-effectiveness assessed
26 for one mild disease subgroup and a severe disease subgroup. As already
27 explained, patients are on average more severely ill in the prevalent cohort than in

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1 the incidence cohort. Therefore we might expect the proportion of patients in the
2 severe disease subgroup that are in the prevalent cohort to be higher than the
3 proportion of patients in the mild disease subgroup that are in the prevalent cohort.
4 In the extreme case, the severe subgroup might represent only patients in the
5 prevalent cohort, and the mild subgroup only patients in the incident cohort. In this
6 case, the ICER for the severe subgroup would equal the prevalent cohort ICER
7 (Equation 3), and the ICER for the mild subgroup would equal the ICER for all future
8 incident cohorts combined (Equation 1). In this special case, the technology might
9 be deemed cost-effective for patients in the incident cohorts, but cost-ineffective for
10 patients in the prevalent cohort, or visa versa. Of course, cost-effectiveness is often
11 assessed without splitting patients into subgroups according to disease severity. For
12 example, in the NICE appraisal of natalizumab for multiple sclerosis, patients in all
13 Expanded Disability Status Scale levels from 0 (mild) to 10 (death) were combined to
14 calculate a single estimate of cost-effectiveness (NICE 2007).²³ In this case, the
15 ICER should be estimated as in Equation 4.

16 We have already outlined two possible areas for future research: the general
17 conditions under which the prevalent cohort ICER is greater than the incident cohort
18 ICER, and vice versa; and the estimation of the sizes of future incident cohorts, and
19 the product life-time of a given technology, and their variability by analysis of trends
20 in the volumes of sales of similar technologies in the past. Now we suggest the
21 following additional areas of research. First, we have shown that cost-effectiveness
22 is influenced by our methods when applied to an example simplified model. Our
23 methods could be applied to other existing cost-effectiveness models to explore their
24 influence on cost-effectiveness. Second, cost-effectiveness for our example model
25 was rather dependent on the specific method used to estimate the costs and benefits
26 for the prevalent cohort. It would be interesting to investigate this for real cost-
27 effectiveness models. Third, we have suggested how clinical effectiveness in our
28 model may be parameterized from trial data. We encourage investigation of the

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1 availability of such clinical data for ‘real world’ models. Fourth, in the previous
2 paragraph, we describe how the proportion of patients in a patient subgroup that are
3 in the prevalent cohort may depend on the subgroup. We recommend investigating
4 the extent to which patient subgroups differ in this respect in real decision problems.
5 Finally, we have assumed that undiscounted incremental costs and benefits are the
6 same for all incident cohorts. Whilst we suggest that this is a reasonable assumption
7 without evidence to the contrary, we encourage investigation into how factors such
8 as the future prices of the health technology²⁴, future changes in the median age at
9 diagnosis, future changes in life expectancy and relative treatment effectiveness may
10 influence this assumption.

11 At present, most economic evaluations of health technologies simulate only
12 the first incident cohort. In this paper, we have argued that model-based economic
13 evaluations should simulate the costs and benefits for *all* people who will be affected
14 by a given health policy decision. In particular, we have (a) demonstrated how to
15 calculate the incremental cost-effectiveness of new health technologies when
16 including the costs and benefits associated with either the current prevalent cohort or
17 the future incident cohorts of patients, or both types of cohort together, and (b), using
18 these equations, we have described the circumstances under which the ‘combined
19 cohorts ICER’ is likely to differ from the ICER for the next incident cohort of patients.

20

21

22 An Excel spreadsheet implementing the example cost-effectiveness model is
23 available from the authors on request.

24

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- 15

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Table 1. Key parameters.

Parameter	Definition
$\Delta K_j, \Delta B_j$	incremental incident cohort cost and benefit between the new and comparator technology at cycle $j = 0, 1, 2, \dots, H$, expressed per patient at the start of the incident cohort
$\Delta C_j, \Delta Q_j$	incremental prevalent cohort cost and benefit at cycle $j = 0, 1, 2, \dots, H$, expressed per patient at the start of the prevalent cohort
K_j, K'_j	incident cohort cost per patient for the new and comparator technology at cycle $j = 0, 1, 2, \dots, H$
C_j, Q_j	prevalent cohort cost and benefit per patient for the new technology at cycle $j = 0, 1, 2, \dots, H$
C'_j, Q'_j	prevalent cohort cost and benefit per patient for the comparator technology at cycle $j = 0, 1, 2, \dots, H$
$K_{t,j}, Q_{t,j}$	future costs and benefits per patient with the new technology for the incident cohort that started in year t (in the past, so that t is negative), j cycles since the start of the incident cohort
H	time horizon of each incident cohort in cycles
r_C, r_B	"inter-generation" annual cost and benefit discount rates $= \frac{1}{1+r_C}, = \frac{1}{1+r_B}$
v_C, v_B	
r^*_C, r^*_B	"intra-generation" cost and benefit discount rates over a cycle

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$$v^*_C, v^*_B = \frac{1}{1+r^*_C}, \frac{1}{1+r^*_B}$$

T expected lifetime of new technology in years

n_t number of patients eligible for the new technology at the start of the incident cohort starting in year $t = -H, \dots, -2, -1, 0, 1, 2, \dots, T$, relative to the number of eligible patients at the start of the first year

p_t probability an eligible patient is given the new technology $t = 0, \dots, T$ years in the future

\bar{p} probability that a patient in the eligible prevalent cohort is given the new technology

N number of patients in the prevalent cohort that are eligible for treatment, relative to the number of patients in the first future incident cohort

A average age of patients at the start of the incident cohort

$s(A, A+t)$ probability a patient who is treated with the comparator technology survives from age A to $A + t$

M number of years over which patients are eligible to be treated with the new technology

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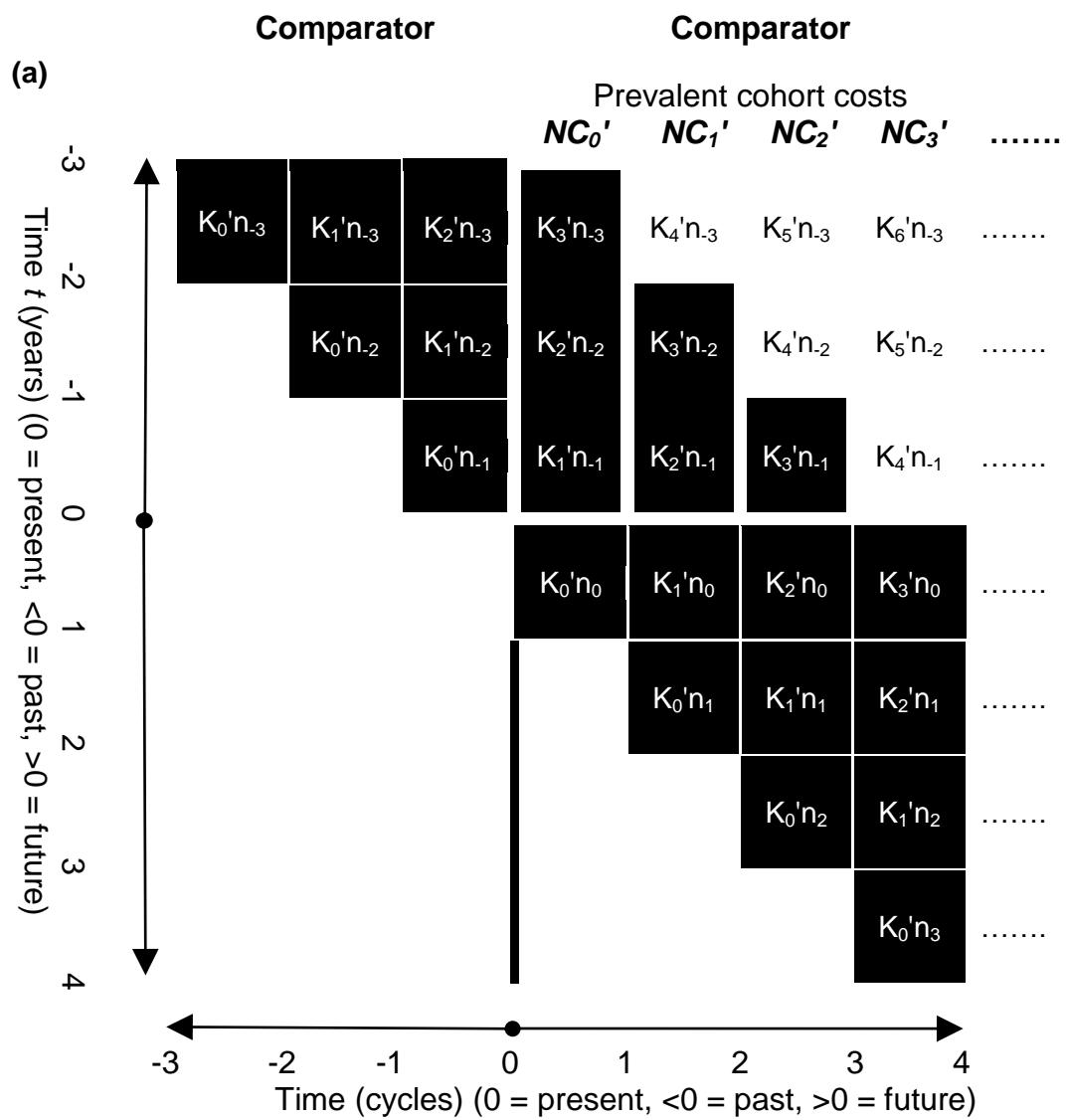
1 **Figure 1.** Prevalent and incident cohort costs for (a) the comparator and (b) the new
2 technology. Incident cohorts are shown as separate rows. For simplicity, one cycle
3 equals one year in this example. Here, the technology is applicable on average to a
4 given patient for $M = 4$ years (4 black cells in each row), and the prevalent cohort
5 comprises $M - 1 = 3$ incident cohorts. The future prevalent cohort comparator and
6 new technology total costs at cycle j , NC_j' and NC_j equal the sum of the costs in the
7 respective highlighted boxes. In (b), all costs before the assessment time (time zero)
8 refer to the comparator technology, because the new technology was not used then.
9 Costs directly associated with the technology occur in some, but not all the black
10 cells. For simplicity, we display costs only four years into the future, whereas the
11 expected technology lifetime, T , will probably be much longer.

12

13 **Figure 2.** Undiscounted costs (£) over time in the example cost-effectiveness model.
14 (a) displays the per patient comparator drug costs showing separately all incident
15 cohorts that started in the past. The costs in the future, i.e. to the right of the vertical
16 line, comprise the costs of the prevalent cohort. For clarity, a single example incident
17 cohort is displayed in bold. Costs initially rise as disease becomes more severe, thus
18 incurring higher health state-related costs. Costs eventually fall to zero as patients
19 die. (b) displays the same data for times in the past, but costs for the new drug in the
20 future, i.e. for the new drug costs in the prevalent cohort. (c) displays comparator
21 drug costs. In (c), the downward sloping line represents total costs in the prevalent
22 cohort (summing over costs in all incident cohorts that started in the past), and the
23 upward sloping line represents total costs in all future incident cohorts. To
24 demonstrate scale, the incident cohorts that make up these quantities, some of which
25 are shown in (a), are just visible at the bottom of the graph. We assume that there
26 are the same number of patients in all incident cohorts.

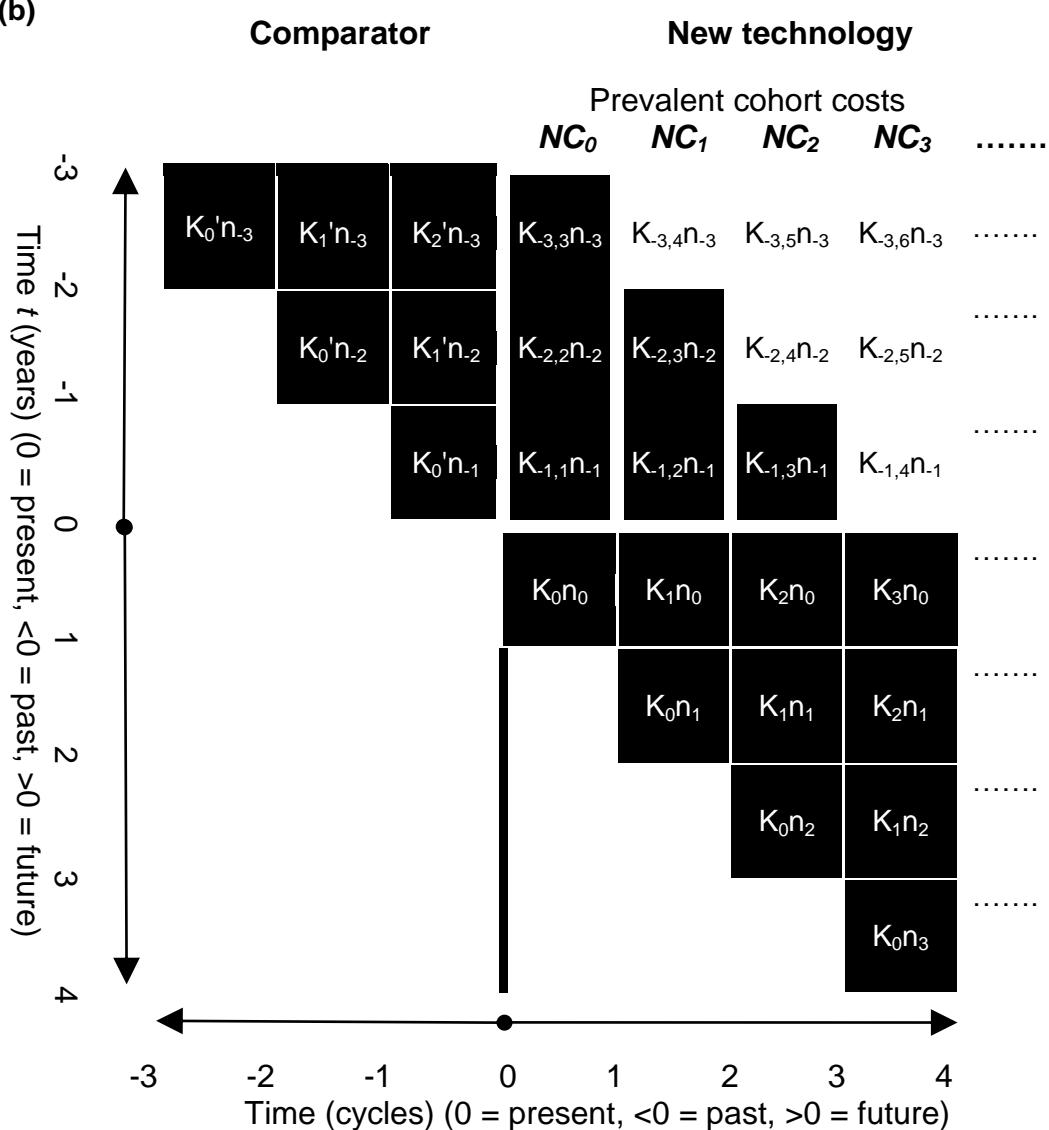
Whose costs and benefits?

Figure 1.



Whose costs and benefits?

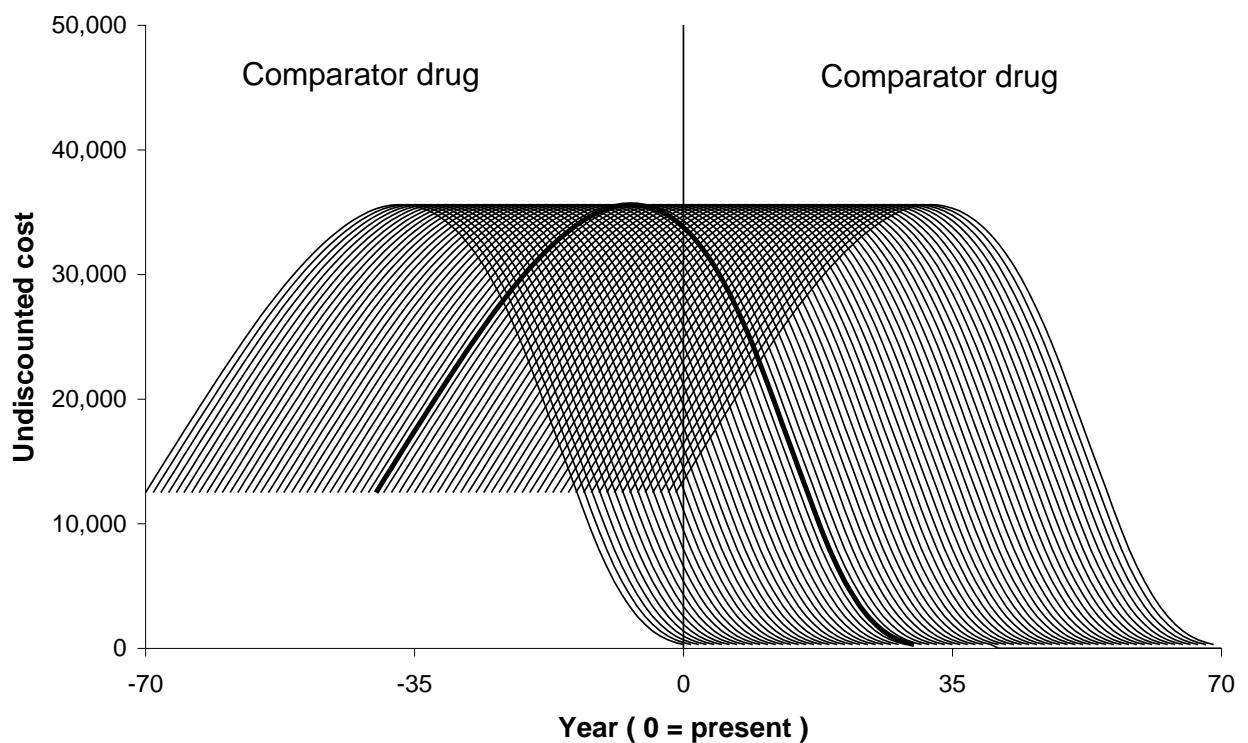
(b)



Whose costs and benefits?

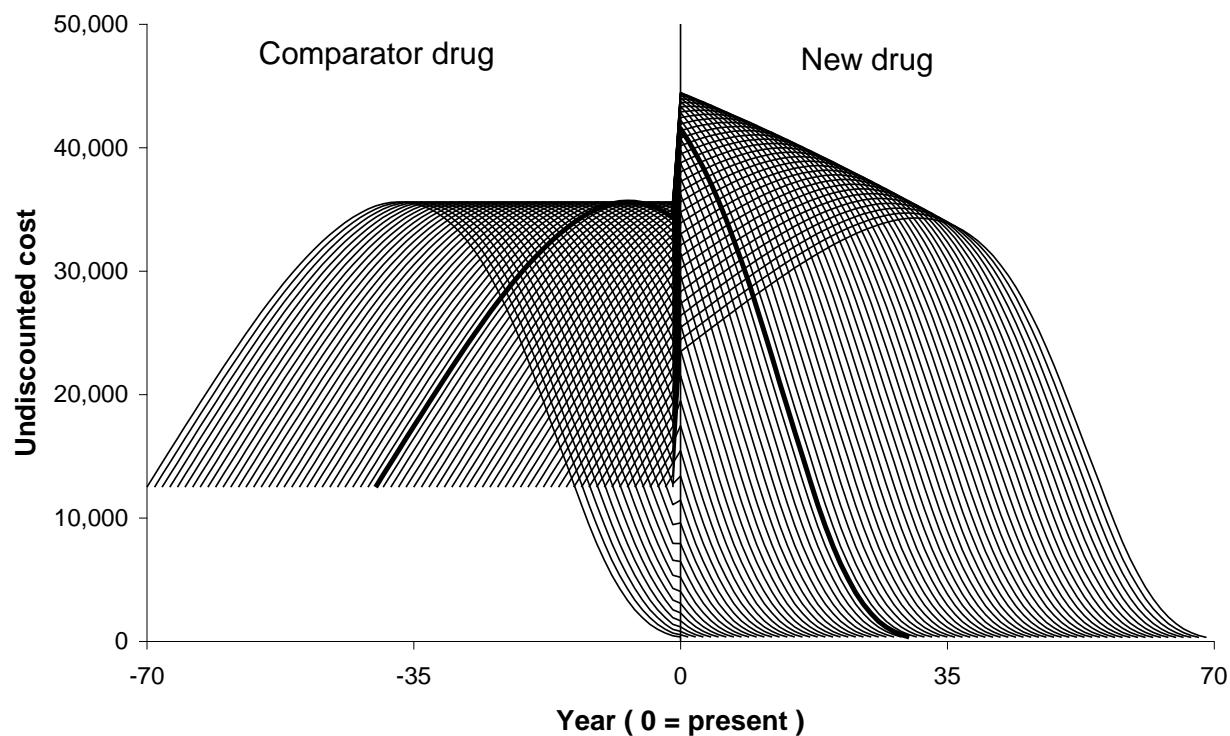
Figure 2.

(a)



Whose costs and benefits?

(b)



(c)

