Concern about some conceptual issues in the construction of Cost Effectiveness Acceptability Curves

(CEACs)

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Section 1 - Introduction

This paper presents a method of displaying uncertainty in cost effectiveness estimates. I refer to them as ALICE curves (Acceptability Levels in Cost Effectiveness Cumulative Probability Curves). Section 2 introduces the concept of iso-acceptability in cost effectiveness ratios. Section 3 discusses the usefulness of a cumulative probability curve in iso-acceptability. Section 4 illustrates how we can use simulated data to produce such a cumulative probability curve. Section 5 compares the approach used in the construction of ALICE curves to that used in the calculation of net benefits. Section 6 describes how uncertainty about the shadow price might be incorporated into the construction of ALICE curves. Section 7 compares Cost Effectiveness Acceptability Curves (CEACs)(1 - 4) with ALICE curves. Section 8 concludes.

Following the main part of the paper there is an appendix in the form of an allegorical story. You may prefer to read this first. It is intended to provide some images that might be useful in conceptualising what would otherwise be rather abstract. The ideas in the main body of the paper and the allegory are linked in the column headed 'rhetorical', which accompanies the allegory.

The abstract for this paper was written when I was feeling more critical of Cost Effectiveness Acceptability Curves than I do now. I still feel that they are inadequate as a means of examining general uncertainty about cost effectiveness estimates, however, they do provide a sensitivity analysis concerning the shadow price of the measure of effect. (The shadow price[] of the measure of effect might most easily be thought of as the value society assigns to a Quality Adjusted Life Year (QALY). To avoid unnecessary repetition the following text refers simply to 'the shadow price').

To avoid confusion, it is perhaps worth stating at the outset, that the concerns I express are not resolved by the point made by O'Brien et al (5) that the current convention of using an accept-rejection criterion that is a straight line through the origin of the cost effectiveness plane when examining uncertainty is problematic. The concern of O'Brien et al relates to asymmetries between willingness to pay for a health gain and willingness to be compensated for a health reduction. I also have concerns about the accept-reject criterion, but for other reasons.

To justify the examination of these issues, we need to believe that cost effectiveness ratios are useful, since, if they are not, it is not helpful to examine the uncertainty surrounding their estimates. I believe that they are useful, because, other things being equal (such as implementation costs), in a world of uncertainty, had I the choice of implementing two projects of similar cost, but different effectiveness, I would first choose to implement the project with the lower cost effectiveness ratio. In an ideal world, where we had perfect knowledge, and where there were no costs incurred in switching between interventions, we would of course immediately implement all interventions where the cost effectiveness ratio is 'better than' than the shadow price of the measure of effect.

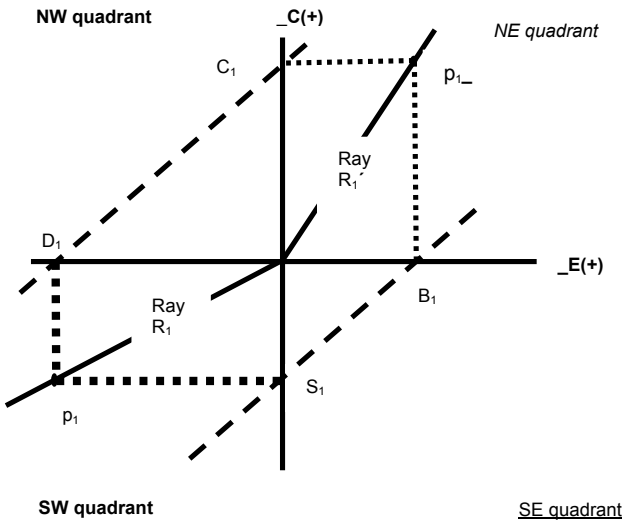
[] "From a welfarist perspective, (the shadow price) is a linkage back to welfare economics and compensation tests, being an estimate of societal willingness to pay (WTP)." O'Brien et al. (See Reference5.)

Section 2 - Iso-acceptability in cost effectiveness ratios

We begin by supposing that we know the shadow price for the measure of effect. This assumption is subsequently relaxed to one in which we have some beliefs about its probability distribution.

Consider the incremental cost effectiveness plane shown in Figure 1. As usual, incremental costs and effects are the differences in costs and effects that arise as a result of switching from one health care intervention to another. I have used the normal convention in which the North-East quadrant displays health gains achieved at an increased cost; the South-East quadrant displays concurrent health gains and cost savings; the South-West quadrant displays reductions in health with cost savings; and the North-West quadrant displays reductions in health at increased cost.

Figure 1 Transposition to iso-acceptable locations in the cost effectiveness plane.



All interventions in the South-East quadrant are acceptable. All interventions in the North-West quadrant are unacceptable. I do not attempt to distinguish levels of acceptability within these quadrants. Assume there is a wide range of potential interventions and that we are indifferent between implementing two small interventions or a single larger one of equal cost effectiveness ratio, hence the size of projects do not affect acceptability. Consider the cost effectiveness ray R_1 in the South West quadrant. We address the question of the position of a cost effectiveness ray in the North-East quadrant of the same acceptability (n iso-acceptable cost effectiveness ratio).

We assume parallel social indifference curves, the gradient of which is everywhere constant and equal to the shadow price of the measure of effect. This is consistent with our usual assumption that we can derive incremental cost effectiveness ratios of equal value regardless of the absolute position that the intervention under consideration and its comparator occupy in cost effectiveness space.

Consider any point p_1 on ray R_1. Using our assumption about the shadow price we can transpose its 'cost' and 'effect' components to the North-East quadrant. The cost saving (S_1) in the South-West quadrant is mapped to a positive health effect (B_1) of equivalent social value. The loss of health or dis-benefit (D_1) in the South-West quadrant is mapped to a financial cost of equivalent social value (C_1). We can use these mappings to construct an iso-acceptable ray $R_1´$.

Iso-acceptable rays 'fan out' from the dominant South-East quadrant, as acceptability levels fall to the completely unacceptable rays on the boundaries of the North-West quadrant. Where the iso-acceptable rays align with the social indifference curves they form a straight line.

If there is asymmetry between willingness to pay for a benefit and willingness to accept for a loss (as suggested by O'Brien et al), this could be represented by two sets of social indifference curves, one in losses and one in gains. Iso-acceptability

lines would be constructed using the appropriate social indifference curves applicable to gains and losses. This possibility is not explored further here.

Section 3 - Cumulative probability curves in iso-acceptability

Figure 2 Cumulative probability of acceptability

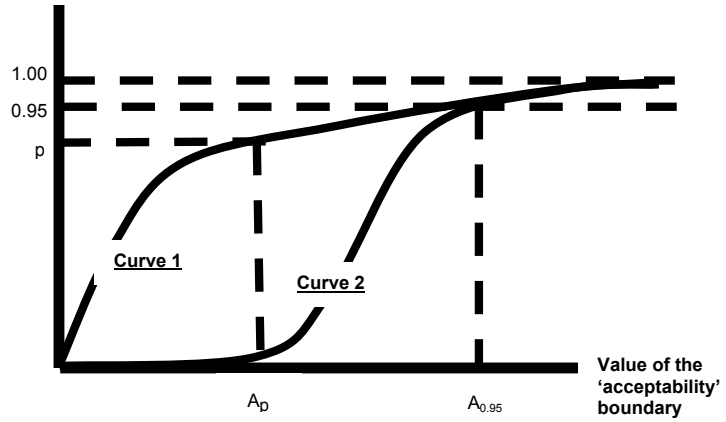


Figure 2 shows two specimen cumulative probability curves. To remind ourselves, these represent estimates of probabilities using repeated simulations from the probability distributions that describe the various estimates used in the estimation of the cost effectiveness of the intervention under consideration. The horizontal axis measures a proxy for acceptability. We will consider below what that proxy might be. For the moment, and to be consistent with other representations of probability in cost effectiveness ratios, assume that we have a measure in which decreasing acceptability is scaled from 0 to infinity with higher numbers representing lower acceptability. The vertical axis shows cumulative probability. The cumulative probability curve is thus interpreted as showing the probability (p) that the cost effectiveness will be at least as good as the limit represented by acceptability value A_p. We are thus able to determine the probability of achieving any specified level of acceptability.

Accordingly, we can read off from the graph the 95% (or other) confidence limit to the estimation of our level of the acceptability. Note that the distributions may differ, even if the 95% boundary is the same. Curve 1 has the same 95% confidence limit as Curve 2, but the former is clearly preferable, showing higher probabilities of achieving the more acceptable results.

The primary intention of the analysis presented here is to provide a way of displaying cumulative probability in acceptability. Only by using such a cumulative probability information can enable decision makers to examine the trade off between probability and acceptability.

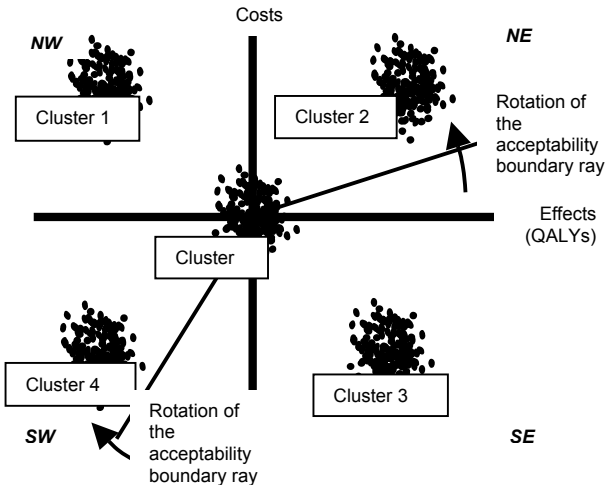
Section 4 - Mapping out Acceptability Levels In Cost Effectiveness (ALICE curves)

In the absence of a direct measure of acceptability, we might use cost effectiveness ratios as a proxy. This presents some difficulties and the potential for confusion. Cost effectiveness simulations of the same numerical values will have different implications for acceptability depending on where they appear in cost effectiveness space. Accordingly, we need to modify cost effectiveness ratios and apply different rules in each of the quadrants to represent the simulation results in terms of equivalent levels of acceptability.

The North-West quadrant

If simulations arise in the North-West quadrant (Figure 3, Cluster 1), none are acceptable since they imply expending more resources to obtain a poorer outcome. In this quadrant, the cumulative probability curve in acceptability curve is not defined. Where only some of the simulations arise in that quadrant (Figure 3, Cluster 5), that proportion forms an upper boundary to the probability of achieving acceptability.

Figure 3 Rotation of acceptability boundary rays.



The South-East quadrant

If simulations arise in the South-East quadrant (Figure 3, Cluster 3) all are acceptable since they imply cost savings and positive health gains. The cumulative probability curve in acceptability would show a value of 1 over the entire range of possible values. Where only some of the simulations fall within this quadrant, that proportions forms a lower boundary to the probability of achieving acceptability.

The North-East quadrant

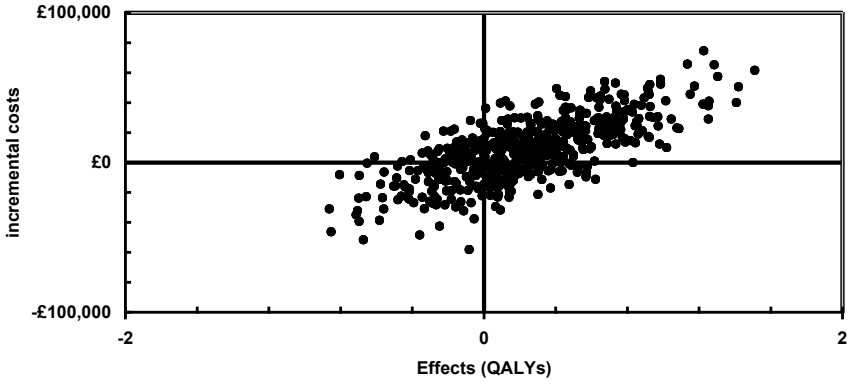
In the remaining two quadrants, we use an Acceptability Boundary (boundary ray for short) and consider its rotation. In the North-East quadrant we rotate the boundary counter-clockwise, thereby considering the effects of increasing the cost effectiveness boundary, and hence applying less stringent acceptability criteria of what constitutes an acceptable event. Probability is estimated by determining the proportion of simulations within the area defined by the boundary ray and boundary with the South-East quadrant. We map out changes in probability as the boundary ray is rotated. The cumulative probability curve derived from the simulations illustrated in Figure 3, Cluster 2 takes the general form of that illustrated in Figure 2 and has a well defined confidence limits.

The South-West quadrant

In the South-West quadrant, the relationship between acceptability and the numerical value of the cost effectiveness ratio is reversed. High values represent high savings or low dis-benefits and are hence more acceptable than low values. Remembering that it is the acceptability levels that we wish to represent on the cumulative probability curve, we need to apply a transformation to represent iso-acceptability by the same numerical values. We have seen in section 2 how these transformations may be determined. It matters little whether we apply the transformation to the boundary rays, or to the simulations themselves. In either case, the effect is the same. Considering the simulations illustrated in Figure 3, Cluster 4, we might map out the probability of achieving acceptability levels, denominated in a way that is commensurable with the acceptability proxy used in the North-East quadrant, by considering the number of simulations lying between iso-acceptable rays and the boundary of the South-East quadrant.

The process would be as follows. For each boundary ray used to construct the cumulative probability curve in the North-East quadrant, use the transformation described in section 2 to determine the iso-acceptable boundary ray in the South-West quadrant. Count the number of simulations lying between that boundary ray and the border between the South-West and South-East quadrants. Express that as the proportion of the total number of simulations and use that proportion as an estimate of the probability of achieving such a level of acceptability. Repeat the process for all boundary rays used to construct the cumulative probability function from data in the North-East quadrant.

Figure 4 Specimen simulations in cost effectiveness space.

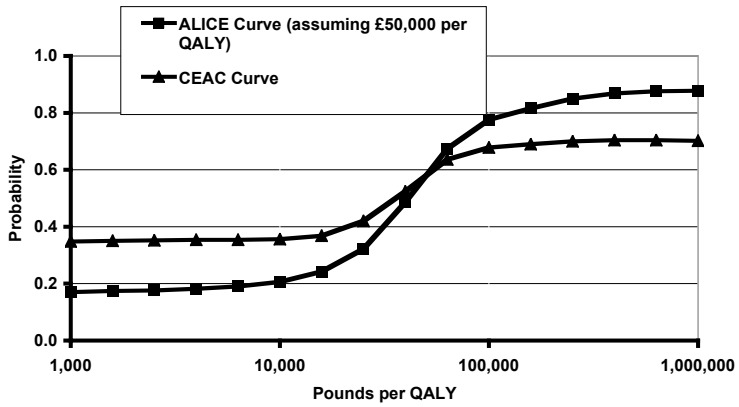


Since the relevant quadrants are now commensurably scaled in acceptability, the results from simulations in all quadrants (as shown in Figure 4, which uses the information in Table 1 to generate simulations) may be combined to construct a cumulative probability curve (Figure 5). This shows equal Acceptability Levels In Cost Effectiveness, hence the acronym ALICE curve. (The CEAC curve shown in Figure 5 is discussed below.)

Table 1 Parameters used in the cost effectiveness simulations

	Intervention Group	Control Group	Incremental values
Mean quantity of input	£ 50,000	£ 40,000	£ 10,000
Standard error of inputs	£ 20,000	£ 20,000	
Mean outcome	0.75	0.5	0.25
Standard error of outcome	0.3	0.3	
Mean cost per QALY	£ 66,667	£ 80,000	£ 40,000
Outcomes explain 50% of variation in costs.			

Figure 5 ALICE and CEAC curves derived from specimen simulations.



Section 5 - Comparison between the approach used in the construction of ALICE curves and Net Cost measures

There are similarities between the transposition of cost effectiveness ratios or rays across quadrants and the construction of net benefit (6 - 8) or net cost statistics. Net benefits and net costs are simple transformations of one another. We consider net costs.

Incremental net costs are calculated as follows:

$$N = C - \$E$$

Where

N = The net incremental cost

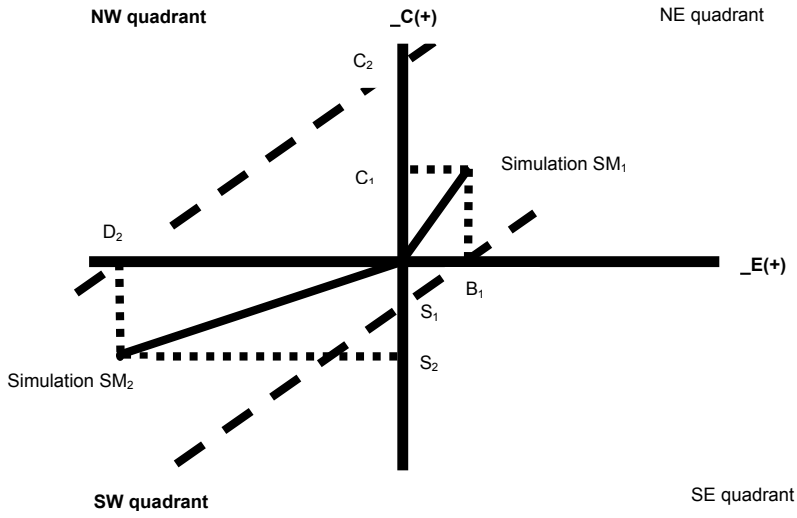
C = The incremental cost

$ = The shadow price of the measure of benefit (I would have used lambda but had problems with the pdf compiler)

E = The incremental effect

Consider the diagram representing the construction of net costs shown in Figure 6.

Figure 6 **Transposition of simulations onto the cost axis to determine net**

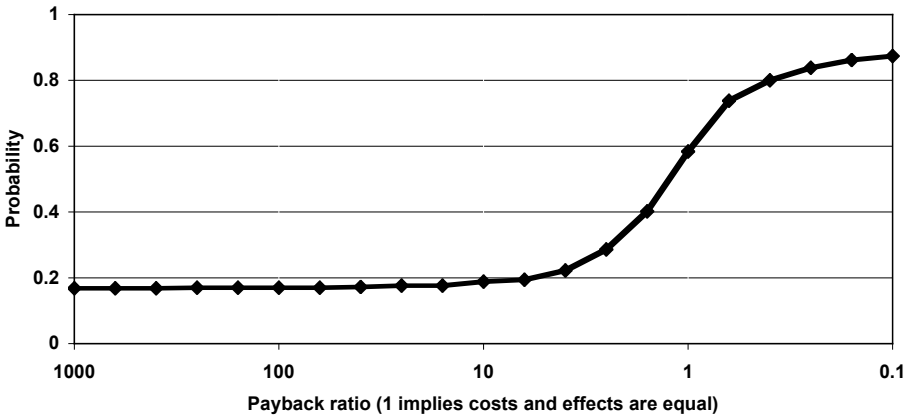


Cost effectiveness simulation SM_1 in the North-East quadrant has costs C_1 and positive effect (benefit) B_1. B_1 is converted into an equivalent monetary value, and is treated as if it were a monetary saving S_1 (savings). The combined value of the monetary cost and the monetary saving is the net cost.

Similarly for simulation SM_2. Cost effectiveness simulation SM_2 in the South-West quadrant has negative 'costs' S_2 (savings) and negative health effect D_2 (dis-benefit). D_2 is converted into an equivalent monetary value C_2, and is treated as if it were a monetary cost. Again the combined value of the monetary cost and the monetary saving is the net cost. In both cases we effectively project the health effects (either positive or negative) onto the 'cost axis'.

Because we conventionally think of cost effectiveness ratios as the ratio of financial costs to health effects, the transformation that I have suggested in Section 4 for the construction of ALICE curves preserves that convention. However, the similarity with the net cost transformation suggests an alternative way of presenting the same information. Just as net costs are calculated as the mathematical sum in costs and effects when both are projected onto the cost axis, so we might calculate the ratio of these values, either as a positive to negative cost ratio, or its reciprocal. The reciprocal (ie the negative cost or 'gains' to positive cost ratio) may have a more intuitive interpretation as the rate of 'payback' for the intervention. Note a payback

Figure 7 An ALICE curve using a payback ratio interpretation of cost effectiveness



ratio of less than unity implies the negative effects are greater than the positive effects. Cumulative probability curves in payback ratios provide an alternative way of presenting information about the probability of obtaining varying levels of acceptability. See Figure 7, which again uses the simulations generated from information shown in Table 1.

Section 6 - Incorporating uncertainty about the shadow price

ALICE curves provide a means of displaying uncertainty concerning acceptability. Ideally they should consider uncertainty arising from all significant sources, including, not only such things as: the use of resources; the cost of those resources; effectiveness; the appropriate discount rate; but also uncertainty about the shadow price (since all these things will influence the acceptability of an intervention). The way in which uncertainty is incorporated into the analysis depends on the precise formulation of the ALICE curve. If acceptability is expressed as 'payback' ratios, we can use some defined probability distribution concerning the value of the shadow price, to project simulated health effects stochastically onto the 'cost' axis.

Section 7 - Cost Effectiveness Acceptability Curves

An early article by van Hout et al (1) describes a CEAC as follows, "…. (it) defines for each predefined C/E-ratio the probability that the C/E-ratio found in the study is acceptable." The process can be visualised in cost effectiveness space as rotating the shadow price from a value of zero to a value of infinity and mapping out the changing proportion of simulations that are acceptable as this rotation occurs. The description of van Hout et al is very similar to the one that I have used to define ALICE curves.

We examine below how CEACS and ALICE curves differ in construction, conception and interpretation. An example of a CEAC is shown in Figure 5. The ALICE curve and the CEAC are constructed from the same simulated data.

Structural differences

1. As already described, there are several equivalent ways to process the data to produce ALICE curves. The method that most clearly demonstrates the contrast with CEACs is the use of an iso-acceptable boundary ray in the South-West quadrant. This rotates clockwise (ie in the opposite direction to the rotation of the boundary in the North-East quadrant) to produce ALICE curves.
2. CEACs make use of the fact that iso-acceptability exists along the shadow price line, extending across both the North-East and South-West quadrants. As a result CEACs use a boundary that is a fixed straight line across both quadrants, and hence one that rotates in the same direction in the North-East and South West quadrants.

3. It follows that ALICE curves only differ from CEACs in their treatment of the South-West quadrant. If no simulations arise there, the curves are identical.
4. Because ALICE curves are constructed by successively expanding the set of simulations that are included, they are cumulative probability curves. (Effectively ALICE curves propagate from the South-East Quadrant and include successively more simulations as the acceptability criterion is relaxed.)
5. CEACs do not successively expand the set of simulations that are counted. As the straight line acceptability ray across the two South-West and North-East quadrant rotates anti-clockwise, it may simultaneously excludes any simulations in the South-West quadrant and include simulations in the North-East quadrant. At a structural level, this explains why CEACs are not cumulative probability curves.
6. It is possible to construct ALICE curves assuming a fixed shadow price for the measure of effect, or specified levels of uncertainty about the value of the shadow price.
7. It is not possible to construct CEACs for a fixed shadow price.

Conceptual differences

8. ALICE curves map out the probability of observing acceptable cost effectiveness ratios in response to changes in the definition of acceptability. (A cumulative probability curve in acceptability.) Acceptability is thus treated as a continuous variable.
9. CEACs map out the probability of observing acceptable cost effectiveness ratios in response to changes in the shadow price of the measure of effect. Acceptability is thus treated as binary, a specific simulation is either cost effective or it is not.

Interpretative differences

10. Figure 5 shows that the CEAC curve has higher probabilities at low costs per QALY than the ALICE curve. At its intercept with the probability axis, the interpretation of the CEAC is that, if the shadow price (ie the social valuation placed upon a QALY) were £1,000, then the probability of the intervention being acceptable would be somewhat less than 0.2. This information has no usefulness if we do not believe that such a shadow price is reasonable. The region of interest of the CEAC is restricted to the region over which there is genuine uncertainty about the appropriate shadow price.
11. Again looking at Figure 5, the interpretation of the ALICE curve at its intercept with the probability axis, is that, given that society values a QALY at some specified value (taken in the example to be £50,000), the probability of the intervention being of acceptability equivalent to one in which we could obtain a QALY by spending only £1,000, is approximately 0.35. Here we may be interested to know how probabilities of acceptability vary over the full range of possible cost effectiveness ratios.
12. The use of a fixed straight line across the North-East and South-West quadrants is justified by its interpretation as the shadow price. It is unequivocally the case that if we specify the shadow price, we can establish which simulations are acceptable. If we specify a different shadow price, some simulations that were formerly acceptable might become unacceptable and vice versa. If a particular shadow price is ‘true’ (ie truly represents the price society is willing to pay to obtain a unit of effect) all others must be false and the probabilities of acceptability under them uninformative. At a

conceptual level this explains why CEACs are not cumulative probability curves.

13. CEACs provide a sensitivity analysis by examining sensitivity to changing the assumptions about the shadow price. (Note that similar approaches might equally be applied to any of the other individual parameters having uncertain values. For example we might map out the probability of observing acceptable simulations in response to changes in the inpatient cost per day, or changes in the discount rate.)
14. ALICE curves represent the effect that general uncertainty in a range of parameters has upon our cost effectiveness estimates.

In short, CEACs vary the shadow price and map out the probability that the intervention would be acceptable or not. ALICE curves fix (or specify uncertainty around) the shadow price and map out the probability of varying acceptability.

Section 8 - Discussion

When van Hout et al (1) state that they are examining the probability that the C/E ratio is acceptable, they are actually talking about the shadow price. While the shadow price is measured in the same units as cost effectiveness, it is not synonymous with it. Cost effectiveness is a phenomenon that describes the intervention. Shadow price is a phenomenon that depends upon public preferences for health care. The two are linked because shadow price, in part, determines the acceptability cost effectiveness estimates.

The issue is further complicated because of ambiguities in the interpretation of cost effectiveness ratios. The complication arises because numerically identical cost effectiveness values may have very different policy implications depending upon where they materialise in cost effectiveness space.

Another area of confusion may arise from our interpretation of the term ‘sensitivity analysis’. It may be helpful to distinguish sensitivity analysis from the analysis of general uncertainty, then consider how these concepts converge somewhat in probabilistic sensitivity analysis. In the first instance, consider them individually.

Simple sensitivity analysis

To facilitate the discussion, I use the phrase ‘performance measure’ to describe the thing that we are interested in estimating (for example the cost per hip operation). Sensitivity analysis examines how responsive the ‘performance measure’ is, to changes in particular parameters. These are referred to as the ‘parameter under investigation’. In its most simple manifestation, sensitivity analysis provides a range of point estimates for our ‘performance measure’ at a range of discrete values for the ‘parameter under investigation’.

Analysis of general uncertainty

Now consider the representation of uncertainty arising from disparate sources. Suppose we have information about the probability functions of a range of key parameters. We can use this information to examine the variability in our estimate of the ‘performance measure’. In acknowledging the variability of these key parameters, we can express the ‘performance measure’ as a stochastic variable and describe its variability. This analysis does not relate variability to a specific ‘parameter of interest’. ALICE curves enable us to examine general uncertainty arising from a range of parameters. By quantifying general uncertainty we may be able to represent this in terms of confidence limits.

Forms of probabilistic sensitivity analysis

It might avoid some confusion if we restrict the use of the term 'sensitivity analysis' to an examination of the sensitivity of our results to changes in individual parameters. Now consider how we might incorporate more sophisticated descriptions of the variability into our examination of the effects of the 'parameter under investigation'. There are two distinct approaches that we might consider. Firstly, we might represent our uncertainty about the 'parameter under investigation' as a probability function and express the resulting estimates of the 'performance measure' as probability function. (Eg the 'parameter under investigation' is the cost per nursing hour which is expressed in terms of its mean and standard error, with a resulting total cost of the intervention, ie the 'performance measure', similarly expressed). In comparison with the simple sensitivity analysis, we substitute probability functions for point values.

Secondly, we might incorporate our knowledge about other key parameters (ie not the 'parameter under investigation'), and express our estimate of the 'performance measure' as a probability function, then examine how the probability function describing the 'performance measure' varies in response to changes in the 'parameter under investigation'. (Eg express the total cost of the intervention in terms of its mean and standard error then examine how they change in response to changed assumptions about the 'parameter under investigation'.)

Both of these approaches examine the influence of a specified 'parameter under investigation' and so both might be appropriately regarded as sensitivity analyses. It is in this second sense that CEACs are a form of sensitivity analysis. In the case of CEACs the probabilistic description of the 'parameter under investigation' is the probability that the intervention has a cost effectiveness value less than the shadow price. The 'parameter of interest' is the shadow price.

As we have seen CEACs and ALICE curves are constructed differently and are capable of doing different things. CEACs are capable of examining sensitivity to varying assumptions about the shadow price, but are not an a satisfactory way of examining uncertainty generally. They do not provide an alternative to conventional confidence interval analysis. ALICE curves are not a method of examining sensitivity to shadow price (or any other single parameter). However they do provide a way of examining general uncertainty concerning a proxy for acceptability in cost effectiveness ratios.

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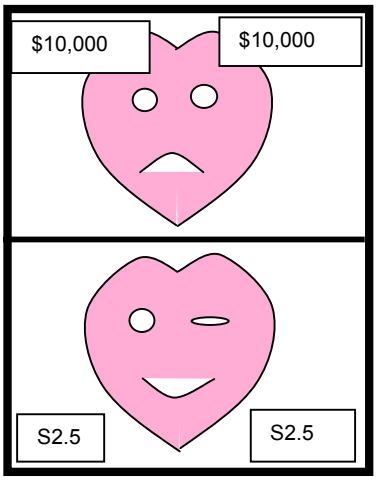
APPENDIX

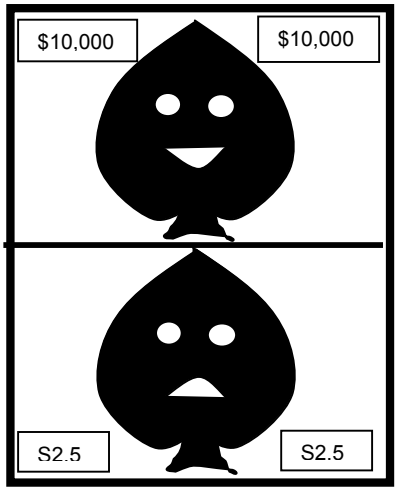
Alice Curve – a tale in four parts[1]

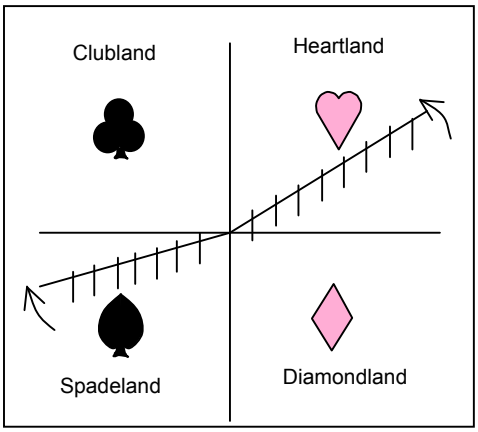
Part 1 Alice finds a friend.

Story – Allegorical	***Commentary - Rhetorical***
Alice's full name is Alice Curve CFC although everyone calls her 'Iso-Alice', she doesn't know why, but it sounds pretty cool. Neither does she understand what CFC stands for but then, that sounds terribly grand. Cool or grand, Alice has a name for all occasions.	Actually 'ALICE CFC' stands for Acceptability Levels In Cost Effectiveness - Cumulative Frequency Curve' ALICE Curves should not to be confused with the similarly titled, but almost completely different, Cost Effectiveness Acceptability Curves (known, rather charmingly, as CEACs). These are not cumulative frequency distributions but provide a way of determining the probability of obtaining an acceptable result under varying assumptions about the shadow price – essentially they providing a sensitivity analysis. ALICE Curves provide a way of examining the probability of obtaining varying levels of cost effectiveness of commensurable acceptability across quadrants (Iso-Acceptability). Sounds similar, but it's not the same.
Alice's job is to count cards when they've fallen from the sky into the big, green meadows that are Heartland. Card showers are the bane of Alice's life. It is probably not quite completely true to say that Alice no more understands her role, than a pea in a jar understands why so many people queue up to stare at it.	Cards represent simulations of cost effectiveness pairs, taken at random using information about their distributions. Counting simulations that meet some acceptability criterion enables us to determine the cumulative frequency curve.
And it can be so boring. All the cards are Hearts (which is why people call where she lives 'Heartland').	Heartland corresponds to the North-East Quadrant in the cost effectiveness plane.
Apart from the fact that they are all hearts, the cards aren't quite like the cards that you and I have seen. Each card has two faces and two different numbers.	The numbers represent the numerical value of the costs and effects.
The top face is a sad face, and the bottom face is a happy face. 	Sad faces represent 'costs', although these are not necessarily monetary costs as we shall see later. Conversely happy faces represent benefits.
Alice always smiles at the happy face, and, as she does the face smiles an even bigger smile back to her, and winks its eye.	Fiction
Now, as I said, Alice's job is to count the cards, but she needn't count them all to begin with, for an unbelievably long fence cuts across Heartland, all the way from the corner where the neighbouring lands join, right out over hills and meadows, for as far as Alice can ever see. Alice	This is the process of determining the probability that cost effectiveness achieves a particular level.

[1] Dedicated to the memory of Douglas Adams

counts all the cards between the neighbouring land to the South and the fence. When she has counted them all, she makes out a report on how many there are, and puts it in an envelope to go to the Chief Censor.	
Then the next day, the Fencers come and move the fence. They work hard to keep the fence in a straight line. It always starts off in the same place, but moves around like the hand on an enormous clock. When the fence has moved, Alice goes round and counts any cards that were previously hidden behind the fence, and fills out another report to tell the Chief Censor just how many cards she can count now.	As the boundary is moved, we can see how probability changes with changing levels of cost effectiveness and hence acceptability.
When the fence has gone all the way round as far as it can go the Croupier comes along and picks them all up again; the fencers move the fence back to where it started from and then the next day all the cards are scattered for Alice to count again.	When all the cards in the North-East Quadrant have been counted the simulation exercise is complete and another study can be undertaken.
Now, I said that there were lands bordering onto Heartland where Alice lives.	Alice is in a land which represents the cost effectiveness plane. She is in the North-East Quadrant.
Alice knows of one country to the South and one to the West. Elsewhere, as far as Alice knows, Heartland just goes on for ever and ever.	To the South is the South-East quadrant. To the West is the North-West Quadrant. Stictly speaking, there is no border with the South-West quadrant although they do meet at the point of intersection.
The country to the South is called Diamondland. "Diamondland would be such a lovely place to live," thought Alice. "For there the cards have two faces, and they are both always smiling."	The South-East Quadrant contains simulations in which there are both cost savings and positive health benefits. Hence the cards have happy faces on the top and the bottom.
To the West of Heartland is Clubland, which is not so nice. Not, as you might suppose, a land full of bright lights and night-clubs, but a land where all the cards have clubs that look as though they might just hit you, and the cards have frowns on both faces, so both faces on every card are sad. Clubland would not be a very nice place to live, thinks Alice.	Conversely for the North-West quadrant.
While Alice is counting the cards, she thinks how big some of the numbers on them are. "The numbers on the cards are sometimes very big," thinks Alice. Next to the happy face the numbers have a letter S next to them. S This stands for Smiles, for here the number counts smiles. Next to the sad face, the numbers have a crossed out letter S which looks like this: $ This stands for 'No Smiles' or 'Dolour' which is an old fashioned word for sadness.	It is important that distances on the different dimensions are measured in different units. Smiles, here representing benefits, might be thought of as QALYs and Dolours, here representing monetary costs are obviously Dollars.
Alice, starts to think how nice it must be in lovely warm Diamondland and starts to get drowsy as she counts the cards and imagines them all jumping over the fence.	Fiction
In no time at all, Alice falls asleep, and as she sleeps, she dreams of digging with a big black spade, down by the corner of Heartland, where the old railway line disappears. And where the walls are so high that Alice cannot look over the top into Diamondland or Clubland. Alice digs and digs until, suddenly she is woken by a white rabbit tickling her face with its whiskers. A shadow crosses the sun, and Alice looks up to see the Magician.	Fiction

He is wearing a long black cape, and a top hat and has a wand in his hand.	
As Alice looks around she sees the hills and fields, which are very similar to those near her own house, in Heartland, but, although there are lots of cards here, the cards are quite different. For a start, they are the wrong colour, here they're black, and the hearts are upside down, and the faces all upside down too, with Smiley faces on the top, and sad faces on the bottom. When she looks closely, she realises that the number on the sad faces are now measured in Smiles, and the numbers on the happy faces are measured in Dolours. "Where am I?" said Alice. "Well, I'd have thought you could guess," said the Magician. "You're in Spadeland. Which is what we call those black, upside down hearts. The top face is the happy face because it has lost sadness, and the bottom face is sad because it has lost its happiness – easy isn't it?" "A good magician could have arranged this without all that digging," thinks Alice.	As we shall see, the fact that the cards are upside down can cause some problems in interpretation. In the South-West quadrant simulations represent cost savings at the expense of lost benefits. Now, the sad face, represents the loss of QALYs and the happy face represents the financial savings. The numbers are now black rather than red. As in normal accounting conventions, colour reverses the sense of the figures (for example, black for profits and red for losses).. 
"Don't be too alarmed," said the Magician. "Some things are upside down here, but some things are the same."	Fiction
Alice smiles, as she always does, at the bottom face on the next card that she sees.	In the South-West Quadrant, a large cost effectiveness ratio is 'good', since is signifies large savings, whereas in the North-East Quadrant it is 'bad'. It requires much mental agility to keep this in mind when interpreting figures, and it makes comparison between the North-East and South-West quadrants quite difficult.
The face scowls back at her and sticks out its tongue.	The cost of mistaking a bad thing for a good thing.
Alice is really upset, but she puts on a brave face. "Don't worry," said the top face on the card, and gave Alice the nicest smile she had ever seen.	Fiction
This cheers Alice up, but she thinks, "It's so hard when you look for a smile and the smile comes from somewhere else. You might miss the smile altogether."	Again emphasising the need for mental agility.
As Alice sat there looking at all the cards in the meadow, she can hear a voice in the distance. The voice that is counting, " … ten thousand four hundred and five, ten thousand four hundred and six, ….. ." "Of course," thinks Alice, "they must have someone here who counts the cards, like I do in Heartland."	Fiction
In the distance Alice saw a little girl, just like herself, so she ran across to say hello. Alice was feeling a little unsure what to do, so she stopped some way away from the girl. "Would she want to talk? Was she too busy? Did she want to be friends? Ah well someone's got to make the first move," decided Alice. Alice smiled and the girl smiled back. "What's your name?" said Alice. "I'm Ecila," said the little girl. Ecila tells Alice all about herself, where she is from and how she got there, and why the land is called Spadeland. Ecila stops counting cards so that she can play with Alice and in no time at all the Magician arranged a picnic, where the white rabbit ate all the lettuce, and the Magician ate all the napkins, but magicked them out from behind Alice's ear.	Obviously Ecila is Alice in reverse, to further emphasise the reciprocal nature of Spadeland.

They had a wonderful picnic with the Magician and even the Fencers (for there were Fencers in Spadeland too)joined in.	
Ecila describes how the Fencers in her country do a similar job as the Fencers in Alice's country, but they move the fence round in the opposite direction.  	Acceptability is inferred from cost effectiveness. In the South-West quadrant, high levels of cost effectiveness now imply high levels of acceptability. To be comparable with the North-East quadrant, where we map out the probability of obtaining less and less acceptable outcomes, the acceptability boundary rotates in the opposite direction. Boundary points at equivalent levels of acceptability can be obtained through a transformation which uses the shadow price, which, for the sake of this argument is assumed as known. See Appendix, Figure 5. Note that this rotation and the resultant bend in the boundary differs from the 'kinky' boundary suggested by O'Brien et al (5). Their boundary is kinky because of possible asymmetries between willingness to pay for a benefit and willingness to accept compensation for a loss. I am suggesting that the boundaries should rotate in opposite directions, so keeping acceptability levels in step.
"It must nearly be teatime," thinks Alice. So she looks at her watch. It says four o'clock. "I hadn't realised it was so late," said Alice, and she checks the time with Ecila whose watch says 8 o'clock. Alice looked very alarmed. "Hey, what is your problem?" laughs Ecila. "We still have 8 hours to go till midnight." Now to understand why Alice was so alarmed, we should understand that in Spadeland watches and clocks go the other way round. At midnight and mid-day, they read 12 o'clock, just the same as your watch and my watch and Alice's watch, but after an hour, watches in Spadeland say 11 o'clock instead of 1 o'clock, then 10 o'clock instead of 2 o'clock etc etc. The reason that clocks and watches in Spadeland go backwards is because they tell how much time you have left of your morning or afternoon, instead of telling you how much you have had. Quite sensible really. "Well," said Alice, "at least they agree four times each day." "It so focuses the mind," added Ecila, "when you know exactly how long you've got left to do things."	There are parallels with the rotation of the acceptability line moving in opposite directions. At the shadow price line, a cost effectiveness ray in the North-East quadrant is numerically equivalent and (arguably) policy equivalent to its opposite ray in the South-West quadrant. In any other position, the same numerical values have different meanings. (See Figure 3 below.)
Alice and Ecila became such good friends that Alice was sad at the thought of leaving. "Why don't you come to Heartland?" said Alice, who was very kind. "The problem is, no one will be here to count the cards if I go," said Ecila.	Fiction (Some might say she was 'all heart'.)
"Don't worry," said the Magician. "If you'd really like to come, I think I can arrange something."	The Magician needs to grapple with the problem of moving the simulations to their equivalent position in the North-East quadrant. See Figure 4.
The Magician called for his friend the Croupier, who always helps the magician with his card tricks. "Croupier," said the Magician, "I wonder if you could cut this pack of fine cards you see scattered around you?" Well, faster than the eye could see, the Croupier began to cut. With a big pair of scissors, the Croupier cut the cards, and as he cut, all the smiling top halves of the cards ran straight to the Diamondland boundary, and all the sad bottom halves of the cards ran straight to the Clubland boundary.	By separating savings and loss of benefits, we can map each to their equivalent position in the North-East quadrant. Using the shadow price, we can convert the financial saving to its equivalent Health Benefit, and the loss of Health Benefit to its monetary equivalent.

Ecila was nearly in tears, “What happens now?” she said. “You madman, how can I count the cards when they’ve all been chopped up and run off?”	Fiction
“Let’s go to the boundary with Clubland, and see what is happening there,” said the magician.	Fiction
The Magician waved his wand and straightaway they were there. It was like one massive airport terminal that stretched along the border as far as Alice could see. Thousands and thousands of cut cards were queuing up, and thousands of little aeroplanes were taking off, some even took off at the same time.	Again see in Figure 4.
“This is crazy,” said Alice. “What stops them crashing into each another?”	Fiction
“That’s the clever thing about the *Shadow Price Airline*,” said the Magician. “The flights are so cheap, because all the aeroplanes fly in straight lines next to one another. So you see, they never, ever crash and we don’t have to worry about air traffic controllers, or radar, or all those complicated and expensive things.”	
The Magician waved his wand again, and in no time at all they were on the other border with Diamondland (for Spadeland, just like Heartland had borders with Clubland and Diamondland as the map above shows) and exactly the same thing was happening.	Illustrating similarity in the treatment of lost benefits and savings.
With a final wave of his wand, Alice and Ecila and the magician were all back safely in Heartland by its border with Diamondland. And here is a funny thing; when Alice tried to say Ecila’s name, it came out backwards. When she tried to say Ecila, it came out as ‘Alice’. Now this can be very confusing as you may know if you have two friends who have the same name, so they decided to call her Alice2.	Fiction. Alice2 standing for the second Alice or Alice as well.
The border here was as frantic as the borders in Spadeland. To the immense relief of Alice2, as they stood and watched, the half cards were getting off the aeroplanes and running as fast as they could to join up again.	Completing the process of expressing the South-West quadrant simulations as their North-East quadrant equivalents. Note transforming the simulations is one way of thinking of the construction of ALICE curves. Using iso-acceptable boundaries is alternative.
And here is another funny thing, now the happy halves were on the bottom, and the sad halves were on the top, just like the red cards in Heartland. This pleased Alice, who knew just which face to smile at now, but it did make Alice2 feel rather odd. And their numbers had changed too, someone had scribbled out the old numbers, and written in new numbers.	Again emphasising how we are conditioned to expect things in certain places. And to expect certain things of numbers. A large cost effectiveness ratio equivalent to an undesirable result. See Figure 4 for the relocation of the simulations in the North-East quadrant. The new numbers are derived through the transformation using the shadow price.
Alice2 was still a bit worried, because she thought that the cards might be standing in the wrong places, and the Fencers get very annoyed when cards don’t stand in <u>exactly</u> the proper place. But the Magician told her not to worry. The numbers on the happy faces are measured in Smiles just like Alice’s cards and the numbers on the sad faces are measured in Dolours and these numbers tell the cards exactly where they should be.	Again refer to Figure 4.
“When it all boils down to it, getting the cards in the right place is just a matter of knowing how many Dolours you are prepared to pay for a Smile,” said the magician, with a twinkle in his eye. But Alice was getting rather tired, and she didn’t really understand properly.	It all depends on the shadow price of a QALY.

Part 2 Alice and Alice2 have to see the Chief Censor.

The next day Alice and Alice2 woke up early as usual. Two letters fell through the letter box when they were having their toast and marmalade. One for Alice and the other for Alice2. Something told the Alices that they were very important. The envelopes had a picture of a big crown in the corner. The letters were from the Chief Censor, and ordered Alice and Alice2 to come to his office – **immediately**. The Chief Censor wanted to know why Alice hadn't done any work yesterday, and whether the reports she had heard about all the cards leaving Spadeland were true.	Fiction
Alice explained what had happened with the magician and said that now that all the cards were in Heartland, and since there were now two people counting them together not just one, they would be much quicker than before. She also pointed out that the Fencers from Spadeland could come across as well and that now they only had one fence to move, they could move it much more quickly. This brought a smile to the Chief Censor's face. She liked the idea of getting the cards counted more quickly. "Magic Megabytes." she exclaimed, which was her favourite saying.	Transferring all simulations to their equivalent position in the North-East quadrant, allows them to be included in a single cumulative frequency distribution in which frequency is measured for the class boundary of cost effectiveness.
Alice asks what the Chief Censor needed all the information for, pointing out that it is good employment practice to tell the workers how their work contributes to the good of the firm.	Fiction
So, the Chief Censor describes how the cards fall out of something called a machine called a Simulator.	For simulation refer to texts such as Briggs Chapter 8 in *Economic evaluation in Health Care* Ed. Drummond and Maguire, OHE, Oxford, 2001.
"Wow, a Simulator Machine sounds very complicated," whispered Alice to Alice2.	Fiction
The Chief Censor ignored this interruption and continued, "Since everyone would like to be in Diamondland, bigger distances away make people unhappy. That is why the unhappy face measures the distance from Diamondland in Dolours." "On the other hand," said the Chief Censor, "people are very happy to be a long way from that nasty Clubland, so the distances from Clubland are measured in Smiles." "Now, a small amount of sadness in exchange for a lot of happiness is better than a lot of sadness for a little happiness."	A low cost effectiveness ratio is more acceptable then a high cost effectiveness ratio. Note, however, that when we are looking at the negatives of these numbers in the South-West quadrant, a low cost effectiveness ratio is less acceptable than high cost effectiveness ratio. Hence, if our intention is to map out the probability of achieving comparable levels of acceptability, we either need to transform the simulations to effectively place them in the North-East quadrant, or derive a transformation of the acceptability boundary in the South-West quadrant.
"Core", said Alice.	Fiction
"Are you paying attention?" said the Chief Censor.	Fiction
"Y y y yesss s s s sir," said Alice, pretending to be afraid.	Fiction
"Well then, if we divide the amount of sadness by the amount of happiness then we get the something called a 'ratio'. It's like the price we pay for a smile."	Determining the cost effectiveness ratio
"What you do is to find out how many Smiles we can buy cheaply, then count again those that we have to pay a little more for and so on and so on," said the Chief Censor. "And that's what the Fencers do, isn't it?" said Alice. "As they move the fence round, then I'm counting cards where the price per smile is getting bigger."	Producing a Cumulative Frequency Distribution as the acceptability criterion is relaxed.
"But when I was in Spadeland the Fencers moved the	In the South-West quadrant there are some significant

Fence in the opposite direction, and there, the number on the happy face was in Dolours, and the number on the sad face was in Smiles," said Alice2. "That can't be right." "Stupid girl," mumbled the Chief Censor. "There is a big difference between Smiles that you get and Smiles that you lose."	reversals. To relax the acceptability criterion requires that it be rotated in the opposite direction (but note, still away from the South-East, and towards the North-West quadrant). What were costs, are now savings hence the smile, and what were QALYs gained are now QALYs lost, hence the frown.
"And that, you see, is why you are called ALICE," said the Chief Censor. But Alice didn't quite see properly.	As described previously.

Part 3 Alice and Alice2 take the train back to Spadeland.

Alice 2 had been staying with Alice for two weeks and they were having a lovely time, but Alice2 needed some of the things that she had left behind in Spadeland.	Fiction
"I'll come with you so we can carry more," said Alice. "Can Useless the Magician come as well?" said Alice2. For that is how the Alices used to talk about the magician. He always seemed to think that he was so clever, and he was great with cards, but at some things he wasn't too hot. He burned the toast, dropped the dishes, and he could never find his wand when you really needed it. So Useless the Magician, and Alice, and Alice2 decided to go back to Spadeland. "I know," said Useless. "Why don't we go the old way - by train?" (Truth to tell, Useless the Magician had lost his wand – again!)	Fiction
As the old steam train rattled down the track, Useless the Magician explains\ed how the track is like a Roman road that goes straight, all the way right into Spadeland and carries on straight all way through, without so much as a kink or a bend for ever. But, although it is straight, in the old days it used to move around a bit like a see-saw. When it was all the way up in Heartland it was all the way down in Spadeland, and when it was all the way up in Spadeland it was all the way down in Heartland. This was very helpful, because, wherever you lived, you could wait for the railway track to swing round to where you were, and then jump on the next train. When the train had gone far enough, you could jump off the train and wait for the railway track to swing round to where you wanted to go to. But now the railway track was getting a bit old and it didn't swing quite as far as it used to.	The railway line represents the shadow price line. Here we are assuming that the shadow price has been more or less fixed by research into its value. The former movement of the railway represents its rotation in determining Cost Effectiveness Acceptability Curves.
As they are going along the train slowed down and stopped. "Why have we stopped?" asks Alice, and she looks out of the window to see some people in purple robes, walking along the track, chanting "Swing the line, the one true line, divider of the world, definer of the faith. Swing the line, the one true line, divider of the world, definer of the faith. Swing the line, the one true line, divider of the world…" etc etc and on and on. Their long robes billowed in the breeze. Incense wafted from golden balls they swung. Their beards were long, but their faces shone with the truth, for they had seen the light. They opened the windows and smiled peacefully at the children. "Help us swing the line, my children." "Who are they?" asks Alice. "They are The Pilgrims of the Railroad," explained Useless. "They want the track repaired so that it can swing around again, just like it used to."	An unnecessary and gratuitous insult at those who have recommended that a previous and more restrained version of this paper be rejected for publication. The pilgrims are people who believe that the only way to examine uncertainty is to keep rotating the shadow price. While there may be uncertainty about the shadow price, to suppose that you can only examine uncertainty in general, by rotating the shadow price to extreme values is ludicrous. Once the shadow price has been determined, the illogicality of rotating the shadow price line should become more apparent. However, it will still be helpful to try to represent uncertainty concerning all the other parameters that have been used in the estimation of the cost effectiveness ratio. ALICE curves provide a way of doing this.
As the pilgrims wave, the train starts off again. All of a sudden, the train shudders and rumbles as the track starts to judder from side to side. Pilgrims are knocked over like skittles, but bounce back, cheering deliriously. Alice and her friend's fly off their seats and end up in a pile of old mattresses on the floor. "What was that?" said Alice. Useless the Magician explained that sometimes the track does shake around a little, but it never moves very far. Not like it used to in the old days. To be continued….	If we do have any residual uncertainty about the precise value of the shadow price, this uncertainty can be dealt with in the same way as uncertainty about all the other parameters. In practice, this might mean applying some stochastic component to the transformation of the boundaries used in the Alice curve (as represented in the story by the shuddering and rumbling of the line as it is randomised to a slightly different alignment), or to the transformation of simulations from South-West to North-East.

Part 4 Alice talks to the mathematician

	Part 4 is a speculative response to critics of the cost effectiveness approach for example Hadorn(9), who has observed that public preferences might support funding expensive interventions, but not funding cheap interventions at the same cost effectiveness level – (a finding that I think we usually regard as a sort of public myopia, but which may by justified under diminishing marginal utility). At present, it remains in the mind of the mathematician so no further commentary is provided
"Well, I'm not sure that they are," said the mathematician (who had a rather peculiar way of talking. "You see, the lines are straight, as long as one Dolour always equals the same number of Smiles. Furthermore, we postulate that, if you have lots of Dolours and lose a few, you don't mind too much 'ceteris paribus', but if you have lots of Dolours and lose them all, then you would be most upset. Ergo, that is why some people take out insurance. They pay a few Dolours, to prevent the risk of losing them all. Quod erat demonstrandum, you see." "And that makes the lines bend?" pondered Alice. "Well, it could do," said the Mathematician. "I think there are some things I will never understand," said Alice, and joined the Fencers, who were throwing Frisbee.	