Full Title: Health Technology Assessment: A Primer for Ophthalmology

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Abstract

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To date, the adoption of health technology assessments, as a way of assessing cost effectiveness, in ophthalmology has been slower, relative to their implementation in other specialities. Nevertheless demands for eye services are increasing due to an aging population. The prevalence of conditions such as glaucoma, cataract, diabetic eye disease, age related macular degeneration increase with age and it is predicted that global blindness will triple by 2050. So there is a challenge for ophthalmologists to ensure that they can contribute to, interpret, critically evaluate, and use findings from economic evaluations in their clinical practice. To aid this, this article serves as a primer on the use of health technology assessments to assess cost effectiveness using economic evaluation techniques for ophthalmologists.

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Introduction

Health systems globally face many challenges that contribute to rising health care costs. In developed countries, growing ageing populations which place increasing demands on all health care services forms one such challenge. Eye care services are no exception owing to the increased prevalence of conditions such as glaucoma, cataract, diabetic eye disease, age related macular degeneration and others amongst those in older age groups. The number of people with blindness and vision impairment is increasing owing to global population growth, coupled with changing age structures, and it is anticipated that global blindness will triple by 2050 [1]. Specifically, given population growth estimates for those over 65 years old the demand for ophthalmology services is anticipated to increase by 5% annually [2]. This rise in health care expenditure will not replace other health care spending but rather contribute to rising total health care expenditure [3].

While vision interventions provides some of the largest returns on investment [4], meeting these health care demands requires resources that in health care are notoriously scarce. The unlimited demands for limited resources means choices must be made and services are often rationed as a result. Economic evaluations and health technology assessments are increasingly used a means to assess the cost effectiveness of health care interventions so as to inform resource allocation decisions.

The pace at which health technology assessments as a way of assessing cost effectiveness have been employed in ophthalmology has been slower relative to their implementation in other specialities [5]. Nevertheless, there have been modest increases in the incorporation of health economics in ophthalmology. In 2008 the European Glaucoma Society reported less than 700 ‘hits’ in PubMed when the

following search terms were searched with glaucoma; ‘cost’, ‘resource’, ‘cost-effectiveness’ and ‘cost-utility’. Repeating this exercise in 2017 yields almost 1100 ‘hits’ in PubMed. Many of these studies only examine costs however and so are not full economic evaluations. This concern has been highlighted previously [5, 6]. Further analysis of search terms on PubMed, considering glaucoma, cataract, diabetic retinopathy and macular degeneration confirms little has changed. There are 3,616 ‘hits’ for these four conditions and cost, resource, cost effectiveness or cost utility between 1966 and June 2017. Of these, 50% were published since 2008. Only 27% were for articles incorporating cost effective or cost utility analyses. See Table 1.

A steep learning curve is thus anticipated as rationing health care continues to dominate public policy formation, health insurers continue to scrutinize claims and out of pocket payments rise for patients. There exists then a challenge for ophthalmologists to ensure that they can contribute to, interpret, critically evaluate [7], and use findings from economic evaluations in their clinical practice. To aid this, this article serves as a primer on the use of health technology assessments to assess cost effectiveness using economic evaluation techniques for ophthalmologists.

Defining Economic Evaluations

Health technology assessments involve examining the medical, economic, social and ethical implications of the development, use and diffusion of a health care intervention or technology. Economic evaluation techniques provide a framework for considering if the benefits accruable from an intervention are worth its costs [8]. Health technology assessments are increasingly being used worldwide as a means of assessing the costs and consequences of competing interventions and thereby informing decisions

regarding which interventions, services, programmes, technologies etc. to finance and/or deliver. In deciding between competing interventions such a systematic approach is needed.

When conducting an economic evaluation, availability, efficacy, effectiveness and efficiency should be considered. Availability determines whether the intervention is accessible to those who need it and who could benefit from it [9]. Efficacy confirms that the intervention works and does more good than harm [9]. Effectiveness describes the success with which the intervention works in real life non-ideal circumstances [9]. Efficiency, by examining the relationship between resource inputs and outputs assesses to what degree the intervention represents value for money.

Types of Economic Evaluation

To conduct a full economic evaluation there must be at least one alternative or comparator and both the benefits and costs must be examined. If these two criteria are not met the evaluation is a partial evaluation. For example, if only the costs of an intervention and current treatment are considered it is a cost analysis.

There are four types of full economic evaluation; Cost Minimisation Analysis (CMA), Cost Benefit Analysis (CBA), Cost Effectiveness Analysis (CEA) and Cost Utility Analysis (CUA). In each, costs are measured in monetary amounts and the difference between them lies in how the benefits are measured.

CMAs are uncommon, as they require that the accruing benefits from each of the interventions under consideration are equivalent. The intervention that delivers with the least cost is then recommended. Complete equivalence between interventions is

rare and as and so economic evaluations which focus on estimating both cost and effect differences are advocated [10].

In CBAs the ‘benefits’ - changes in welfare, are measured in monetary units. As both the benefits and costs are measured in monetary amounts the net benefit can be estimated; Net Benefit = Benefits – Costs. If net benefit is positive i.e. benefits exceed costs, the intervention is considered cost effective. If the net benefit is negative i.e. costs exceed benefits, the intervention cannot be considered cost effective. Estimating health outcomes in monetary units is however challenging.

In CEAs the benefits of an intervention are expressed in natural health units such as life-years gained, symptom free days or days of disability avoided etc. A disadvantage is that CEAs can only be used to compare interventions that produce a common health effect.

In light of this CUAs emerged. Herein the benefits are measured using a measurement that represents quality of life – Quality Adjusted Life Years for example.

In both CEA and CUA the incremental costs of the intervention and comparator are compared to the incremental benefit using a Cost Effectiveness Ratio; (Cost Intervention - Cost Comparator) / (Benefits Intervention - Benefits Comparator). If the intervention is less costly and more effective i.e. generates more benefit than the comparator, it can be considered cost effective. Alternatively, if the intervention is more costly and less effective than the comparator it cannot be considered cost effective. If the intervention is more costly and more effective an estimate of what society is willing to pay for the additional unit of effectiveness is required to determine if the additional benefit is worth the additional cost.

Conducting an Economic Evaluation

As before, for an economic evaluation to be a full economic evaluation a comparator is needed. This represents an appropriate alternative to the intervention or technology under consideration. Usually the comparator is typical or usual care. For novel interventions, technologies or programmes the comparator may be more simply to ‘do nothing’.

The perspective for the evaluation then needs to be considered. Given the foundation of economic evaluations is welfare economics, economic evaluations should, in theory, be undertaken from a societal perspective. However, as evaluations are often requested or commissioned by health payers theirs is often the only perspective sought. This is considerably narrower than a societal perspective and risks excluding relevant benefits and costs accrued, some of which may be to the patient, so caution should be exercised.

Estimating Costs and Benefits for Economic Evaluation

When estimating costs all relevant resources associated with the intervention and its comparator need to be identified, measured and valued [9]. Costs occurring in the future will need to be discounted to account for time preference. Applying a discount rate has the effect of giving less weight to benefits and costs occurring in the future. National guidelines should be consulted for instructions on which discount rate to use, calculating depreciation on assets, associated labour costs, overhead and exchange or inflation rate calculations as required. Relevant overheads should also be included.

When estimating benefits the methods used depend on the type of economic evaluation being employed. In CBAs, benefits, reflecting changes in welfare, are

measured in monetary amounts, which can be measured by a variety of means. The equivalent variation method estimates the income adjustment necessary to reflect changes in consumer utility that would occur if an event, for example blindness, occurred. The compensating variation method estimates the income adjustment that returns the consumer to the original utility after an event has occurred. Willingness to pay techniques estimate the maximum amount that an individual would be willing to sacrifice so as to achieve a desired state of health or to avoid an undesirable state of health. Each of these methods requires extensive data collection and are, as a result, under-utilized in health technology assessment.

Much of the empirical literature for economic evaluations and/or health technology assessments employ CEAs wherein benefits are measured as natural health units or CUAs wherein benefits are measured using utility measurements such as Quality Adjusted Life Years. The latter are used predominantly in the United Kingdom, other European countries and Canada, who have determined willingness to pay estimates for units of effectiveness and advocate their use. Here, generic preference based instruments that measure health related quality of life such as the EQ-5D developed by EuroQol are advocated. Alternatively condition specific measures, such as the National Eye Institute 25-item visual function questionnaire (VFQ-25), may be used and mapped onto generic preference based instruments to generate QALYs, using bespoke algorithms. The VFQ-25 is a 25-item version of the 51-item National Eye Institute Visual Function Questionnaire (NEI-VFQ), developed with the goal of creating a survey that would measure the dimensions of vision targeted health that are most important for persons who have chronic eye diseases [11].

As with costs, benefits accruing in the future need to be discounted to account for time preference using appropriate discount rates. Again, national guidelines typically detail instructions for discounting.

Identifying Evidence

Evidence for benefit and cost estimates of interventions and comparators may be readily available to populate an economic model, if the economic evaluation is being conducted alongside a clinical trial, for example. However, it is often the case that evidence from a variety of sources will need to be gathered and extrapolated into the future to consider all relevant comparators for a relevant time period. As a result the use of Decision Analytical Modelling to complement Economic Evaluations has evolved [12, 13].

Decision Analytical Modelling

Decision Analytical Modelling employs quantitative methods to systematically examine the clinical, epidemiological and economic evidence of an intervention and its comparator. This generates a precise point estimate for the benefits and costs as well as enabling an examination of the uncertainty surrounding the decision under review and its outcome [14].

Decision Analytical Modelling can be used to extrapolate beyond time points observed in a trial, link intermediate endpoints to final outcomes; generalize outcomes to other settings and synthesize comparisons between alternatives where trials are non-existent [12].

While no amount of modelling can fully offset the gaps in available evidence, decision analytical modelling can provide point estimates for economic evaluations and permit valid statistical analysis of data to inform such evaluations [9, 12].

While there are many types of decision analytical models, the simplest and most common are decision trees. These graphically represent the 'prognosis' of alternative interventions using pathways. They are useful for simple models (no time dependency for example), with short time horizons or multifaceted value structures [9, 15, 16]. State transition models are also popular. Decision problems are conceptualized in terms of a set of health states and transitions between those states for a particular condition. The most common type of state transition model employed is a Markov Model [14]. These represent random processes that occur over time using cycles [17] and are useful for handling disease complexities and managing benefits and costs simultaneously, as well as facilitating the estimation of QALYs [17, 18] and cohort simulations.

Handling Uncertainty

In every economic evaluation and its decision analytical model when used, uncertainty exists. Uncertainties are costly and increase the risk of making incorrect recommendations regarding the cost effectiveness of an intervention. This can exert costs on society owing to exposure to interventions that are later demonstrated to be ineffective and/or delayed access to beneficial treatments/programmes. Reversing incorrect decisions is also costly. Thus, uncertainty must be accounted for when conducting economic evaluations.

Uncertainty includes first order uncertainty owing to structural uncertainty associated with assumptions made in the model, random variability in outcomes between identical

patients, and uncertainty surrounding parameter estimates employed [14]. Structural uncertainty can be examined using sensitivity analysis, for example scenario analyses can be used to examine the impact of the assumptions used. Parameter uncertainty can be examined using deterministic sensitivity analysis also. For large models with correlated parameters etc. probabilistic sensitivity analyses are more practical. These provide a means of addressing joint uncertainty in a model. By incorporating uncertainty from input parameters, uncertainty on output parameters can be described [14]. To conduct a probabilistic sensitivity analysis, uncertainty in input parameters need to be characterized first. This uncertainty is propagated through the model using a Monte Carlo simulation. The implications of uncertainty can then be presented [14].

Presenting Cost Effectiveness Results

Cost Effectiveness Plane

A Cost Effectiveness (CE) Plane is a four-quadrant diagram that illustrates the incremental costs and effects of an intervention compared to an alternative [19]. The incremental costs are plotted on the vertical axis and the effects on the horizontal axis. Figure 1 presents an example of a CE plane. If the intervention is more effective i.e. generates more benefit and is less costly than the comparator its point estimate will fall in the Southeast quadrant. Here the intervention is considered cost effective and is dominant. Alternatively, if the intervention less effective i.e. generates less benefit and is more costly its point estimate will fall in the Northwest quadrant. Here the intervention is not considered cost effective and is dominated. Where the intervention is more effective and more costly its point estimate will fall in the Northeast quadrant. An estimate of what society is willing to pay for the additional unit of effectiveness is required to determine if the additional benefit is worth the additional cost. If the

intervention is less effective and less costly its point estimate will fall in the Southwest quadrant.

Where a probabilistic sensitivity analysis has been performed the results of the simulation will yield a large number of points, which can be plotted in a similar fashion to what is shown in Figure 1. The distribution of these points amongst the four quadrants illustrates the existence and extent of uncertainty in incremental costs and effects. These results are represented by the 'cloud' of points on Figure 2.

Incremental Cost Effectiveness Ratio (ICER)

The Incremental Cost Effectiveness Ratio (ICER) provides a measure of additional cost per additional unit of health gain produced by the intervention compared to its comparator in CEAs and CUAs. The ICER is estimated as the additional cost (ΔC) of the intervention compared to its comparator divided by the additional health gain or benefit (ΔE); ICER: ΔC / ΔE [20]. Where a probabilistic sensitivity analysis is performed the average of the expected benefits and costs can be used to estimate the ICER.

The ICER can be compared to an external threshold value or ceiling ratio (RT), which represents the maximum society is willing to pay for an additional unit of effect or health gain. The diagonal dashed line on figure 1 presents this cost effectiveness threshold with the slope of a line drawn between the origin and point A i.e. OA representing the ICER. Figure 1 shows that the ICER associated with point A is less than the threshold so this intervention can be considered cost effective.

Incremental Net Benefit

The incremental net benefit (INB) is an alternative to the ICER. In CBAs, the INB can be estimated straight forwardly as both the costs and benefits are measured in monetary amounts. In CEAs or CUAs however the benefits need to be translated into monetary amounts. This can be done using the ceiling ratio. Previously, if $\Delta C / \Delta E < RT$ the intervention is cost effective. If we re-arrange the formula it can be said that the intervention is cost effective if the INB is positive. The INB is the change in effects multiplied by the ceiling ratio less additional costs; ICER, $RT * \Delta E - \Delta C < 0$. For the net benefit to be positive the monetary benefit must be greater than additional costs; $RT * \Delta E < \Delta C$.

Cost Effectiveness Acceptability Curve (CEAC)

CEACs summarise uncertainty surrounding the cost effectiveness decision for various ceiling ratios [21-23]. Recalling from the ICE Plane, co-ordinates that fall below and to the right of the line, representing the ceiling ratio, indicate the intervention is cost effective compared to the comparator. When a probabilistic sensitivity analysis is employed, the Monte Carlo simulation yields multiple co-ordinates. When these are plotted the probability of the technology being cost effective can be estimated as the number of co-ordinates falling in this region as a proportion of the simulation size. This can be repeated for all potential ceiling ratio values to represent different willingness to pay thresholds. The probability of the intervention being cost effective associated with each ceiling ratio is plotted on the CEAC. For example, if on an ICE Plane at a ceiling ratio of €45,000/QALY, 6% of the co-ordinates lie in the cost effectiveness region then there would be a 6% probability that the intervention is cost effective and a 94% probability that the alternative is cost effective. This is repeated for a range of ceiling ratio values and plotted to form the CEAC. Figure 3 illustrates this example.

Discussion

Challenges in Implementing Economic Evaluations and/or Health Technology Assessments in Ophthalmology

The methods described above are standard methods employed to conduct economic evaluations. They are robust and verified. However, a ‘one-size-fits-all’ approach may not apply. Individual clinical and therapeutic areas must consider how to implement them. A key challenge is the sensitive measurement of health outcomes in a meaningful way particular to a clinical or therapeutic area.

Kymes [24] questioned how deteriorating vision and its impact on quality of life should be measured appropriately. Furthermore, given their sensitivity and responsiveness, the suitability of existing generic quality of life instruments like EQ-5D, to measure the impact of vision and its deterioration on quality of life has been debated [24, 25]. Others [26] were concerned with how to measure quality of life over the duration of a disease – particularly when quality of life may be impacted greater in the later stages of diseases. They also had concerns with respect to gathering evidence with ethical concerns regarding the use of randomized controlled trials and the procurement of sufficient sample sizes [26].

Opportunities for Implementing Economic Evaluations and/or Health Technology Assessments in Ophthalmology

The challenges surrounding measuring quality of life over the lifetime of a disease or for a particular patient population such as the visually impaired and collecting evidence are not unique to ophthalmology. Similar data collection issues are present in many

clinical and therapeutic areas – particularly where non-drug interventions are being considered.

While the economic evaluation techniques discussed in this primer are predominately associated with drugs their foundations go beyond this. The incorporation of decision analytical modelling provides a means of overcoming some of the challenges listed above. This permits the extrapolation of data beyond that observed in trials, linkage of intermediate clinical endpoints to final outcomes, the generalisation of outcomes to other settings and the synthesis of head-to-head comparisons where relevant trials are non-existent thereby offering a means to inform decisions in the absence of mature data [12].

Likewise, measuring health outcomes so that they are sensitive has been experienced in many areas, including mental health. Often condition specific instruments are mapped onto generic ones, such as VFQ-25. While this is not the ideal it is suitable and attempts have been made to do this in ophthalmology [27, 28].

The Food and Drug Administration Agency (FDA) and other regulators have ensured that drug interventions have sufficient evidence to populate economic models. Provisions to extend this to medical devices are underway. Prior to this, assessments of medical devices were limited to using evidence from early cases, registries etc. This evidence was synthesized and extrapolated to estimate cost effectiveness using decision analytical modelling. Such a strategy can be adopted for ophthalmological health care interventions as health technology assessments (HTAs) develop.

It has been suggested that ophthalmological economic evaluations and HTAs incorporate synergies created from simultaneously screening for multiple diseases in primary care; as well as patient preferences and simultaneously consider the cost

effectiveness of preventative care [24]. Capturing and valuing such synergies, along with incorporating preventative care and patient preferences are priorities for all clinical areas. There is an opportunity for ophthalmology to lead the way in how to achieve these priorities.

Conclusions

The challenges facing health care systems worldwide - changing demographics, a rapid pace of change and the development of new technologies are only going to intensify. While ophthalmology has come to the table later with respect to requirements for formal economic evaluations it has not been immune to budget cuts etc. Ophthalmology needs to be ready and able to engage with health economists to prepare, interpret, critically evaluate and use findings of economic evaluations and health technology assessments.

Figure 1. A cost effectiveness (CE) plane is a four-quadrant diagram that illustrates the incremental costs and effects of an intervention compared to an alternative. The incremental costs are plotted on the vertical axis and the effects on the horizontal axis.

Figure 2. The incremental cost effectiveness (ICE) plane is four quadrant diagram that plots uncertainty surrounding costs and effects of an intervention compared to its alternative. Where a probabilistic sensitivity analysis has been performed the results of the simulation will yield a number of points, which can be plotted in a similar fashion to what is shown in figure 1. The distribution of these points amongst the four quadrants illustrates the existence and extent of uncertainty in incremental costs and effects. These results are represented by the 'cloud' of points (using results of the Monte Carlo simulation).

In this example, there is no uncertainty surrounding the existence of differences in costs, intervention is more expensive than current practice. But there is uncertainty surrounding the extent of this uncertainty; additional costs vary between €18 and €708 (vertical axis). There is uncertainty surrounding the existence and extent of differences in effects with additional benefits varying between -0.06 and +0.05 QALYs (horiztonal axis).

Figure 3. Cost effectiveness acceptability curves summarise the uncertainty surrounding the cost effectiveness decision for various ceiling ratios using the Monte Carlo simulation results (presented on the CE plane) results. For example, if on the ICE plane at a ceiling ratio of €45,000/QALY, 6% of the co-ordinates lie in the cost effectiveness region then there would be a 6% probability that the intervention is cost effective and 94% probability that current practice is cost effective. This is repeated for a range of ceiling ratio values and plotted to form the CEAC.

References

1. Bourne, R.R.A., et al., *Magnitude, temporal trends, and projections of the global prevalence of blindness and distance and near vision impairment: a systematic review and meta-analysis.* The Lancet Global Health. **5**(9): p. e888-e897.
2. Pinto, J., *Major Ophthalmic Industry Trends.* Ophthamology Management, 2011. **September**.
3. Galor, A., et al., *Influence of socio-demographic characteristics on eye care expenditure: data from the Medical Expenditure Panel Survey 2007.* Ophthalmic epidemiology, 2015. **22**(1): p. 28-33.
4. Brown, M.M., et al., *Financial return-on-investment of ophthalmic interventions: a new paradigm.* Current Opinion in Ophthalmology, 2014. **25**(3): p. 171-176.
5. Kobelt, G., *Health economics, economic evaluation, and glaucoma.* Journal of glaucoma, 2002. **11**(6): p. 531-539.
6. Coyle, D. and M. Drummond, *The economic burden of glaucoma in the UK.* Pharmacoeconomics, 1995. **7**(6): p. 484-489.
7. European Glaucoma Society, *Terminology and guidelines for glaucoma.* . 3rd Edition ed. 2008: Editrice Dogma.
8. Banta, H.D. and B.R. Luce, *Health care technology and its assessment: an international perspective.* 1993.
9. Drummond, M.F., et al., *Methods for the economic evaluation of health care programmes*. 2015: Oxford University Press.
10. Briggs, A.H. and B.J. O'Brien, *The death of cost-minimization analysis?* Health economics, 2001. **10**(2): p. 179-184.

11. Mangione, C.M., et al., *Development of the 25-list-item national eye institute visual function questionnaire.* Archives of Ophthalmology, 2001. **119**(7): p. 1050-1058.
12. Buxton, M.J., et al., *Modelling in ecomomic evaluation: an unavoidable fact of life.* Health economics, 1997. **6**(3): p. 217-227.
13. Glick, H.A., et al., *Economic evaluation in clinical trials*. 2014: OUP Oxford.
14. Briggs, A.H., et al., *Model parameter estimation and uncertainty: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-6.* Value in Health, 2012. **15**(6): p. 835-842.
15. Roberts, M., et al., *Conceptualizing a model a report of the ISPOR-SMDM modeling good research practices task force–2.* Medical Decision Making, 2012. **32**(5): p. 678-689.
16. Sonnenberg, F.A. and J.R. Beck, *Markov models in medical decision making a practical guide.* Medical decision making, 1993. **13**(4): p. 322-338.
17. Briggs, A. and M. Sculpher, *An introduction to Markov modelling for economic evaluation.* Pharmacoeconomics, 1998. **13**(4): p. 397-409.
18. Briggs, A., M. Sculpher, and K. Claxton, *Decision modelling for health economic evaluation*. 2006: OUP Oxford.
19. Black, W.C., *The CE plane a graphic representation of cost-effectiveness.* Medical decision making, 1990. **10**(3): p. 212-214.
20. Stinnett, A.A. and A.D. Paltiel, *Estimating CE Ratios under Second-order Uncertainty The Mean Ratio versus the Ratio of Means.* Medical decision making, 1997. **17**(4): p. 483-489.

21. Fenwick, E., K. Claxton, and M. Sculpher, *Representing uncertainty: the role of cost-effectiveness acceptability curves.* Health economics, 2001. **10**(8): p. 779-787.

22. Fenwick, E., B.J. O'Brien, and A. Briggs, *Cost-effectiveness acceptability curves–facts, fallacies and frequently asked questions.* Health economics, 2004. **13**(5): p. 405-415.

23. O'Brien, B. and A. Briggs, *Analysis of uncertainty in health care cost-effectiveness studies: an introduction to statistical issues and methods.* Statistical Methods in Medical Research, 2002. **11**(6): p. 455-468.

24. Kymes, S.M., *The State of Economic Evaluation in Vision Research—Adding a fourth for bridge.* Ophthalmic epidemiology, 2015. **22**(1): p. 1-3.

25. Kymes, S.M., *Is it time to move beyond the QALY in vision research?* Ophthalmic epidemiology, 2014. **21**(2): p. 63-65.

26. Tuulonen, A. and H. Sintonen, *Health economics, cost-effectiveness, and glaucoma care*, in *Glaucoma*. 2006, Springer. p. 123-133.

27. Kay, S. and A. Ferreira, *Mapping the 25-item National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25) to EQ-5D utility scores.* Ophthalmic epidemiology, 2014. **21**(2): p. 66-78.

28. Browne, C., et al., *Estimating quality-adjusted life years from patient-reported visual functioning.* Eye, 2012. **26**(10): p. 1295-1301.

Figure Legend

Figure 1. The Cost-Effectiveness Plane

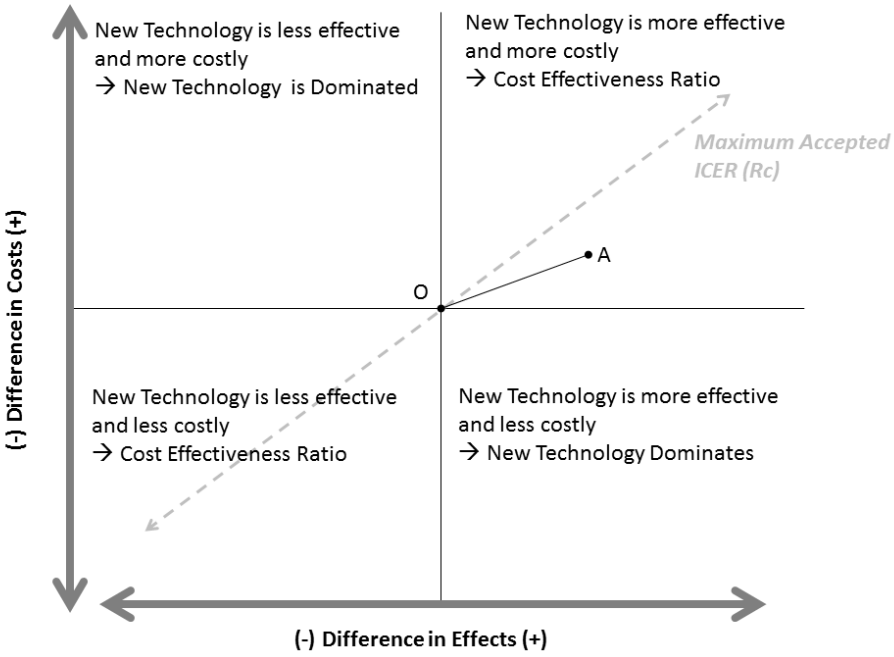

Figure 1. A cost effectiveness (CE) plane is a four-quadrant diagram that illustrates the incremental costs and effects of an intervention compared to an alternative. The incremental costs are plotted on the vertical axis and the effects on the horizontal axis.

Figure 2. Sample Cost Effectiveness Plane from Probabilistic Sensitivity Analysis

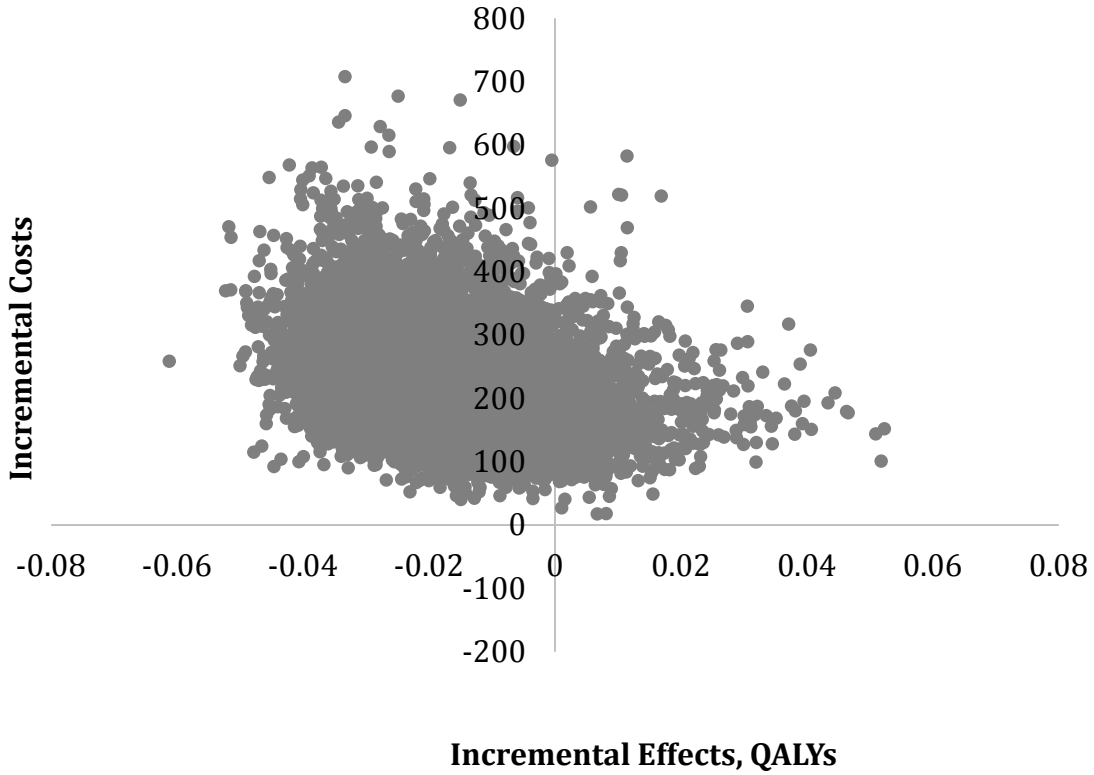

Figure 2. The incremental cost effectiveness (ICE) plane is four quadrant diagram that plots uncertainty surrounding costs and effects of an intervention compared to its alternative. Where a probabilistic sensitivity analysis has been performed the results of the simulation will yield a number of points, which can be plotted in a similar fashion to what is shown in figure 1. The distribution of these points amongst the four quadrants illustrates the existence and extent of uncertainty in incremental costs and effects. These results are represented by the 'cloud' of points (using results of the Monte Carlo simulation).

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surrounding the extent of this uncertainty; additional costs vary between €18 and €708 (vertical axis). There is uncertainty surrounding the existence and extent of differences in effects with additional benefits varying between -0.06 and +0.05 QALYs (horiztonal axis).

Figure 3. Sample Cost Effectiveness Acceptability Curve

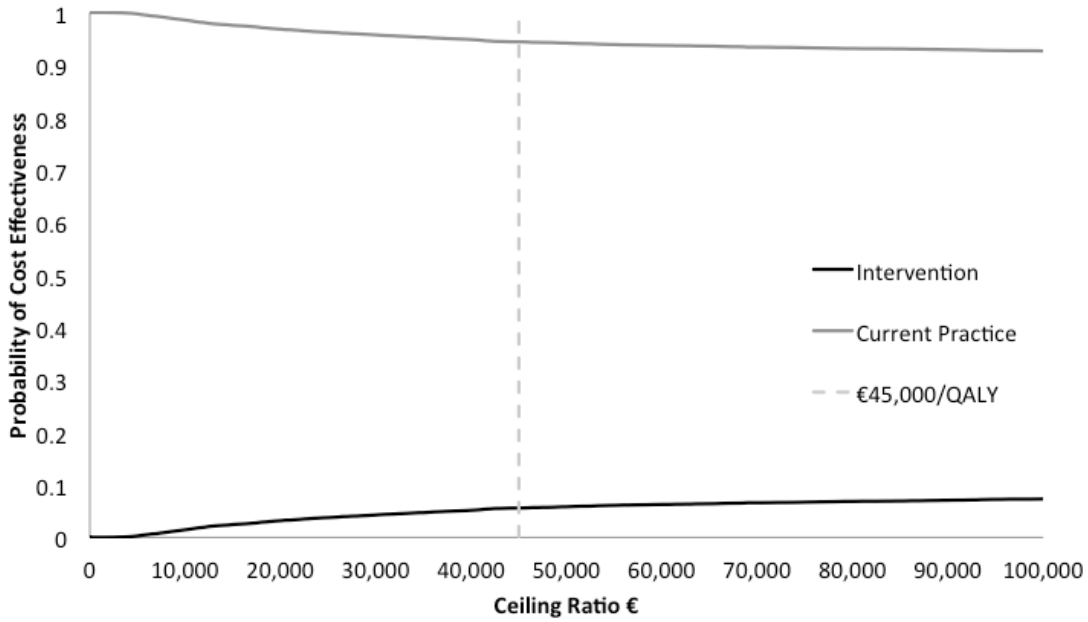

Figure 3. Cost effectiveness acceptability curves summarise the uncertainty surrounding the cost effectiveness decision for various ceiling ratios using the Monte Carlo simulation results (presented on the CE plane) results. For example, if on the ICE plane at a ceiling ratio of €45,000/QALY, 6% of the co-ordinates lie in the cost effectiveness region then there would be a 6% probability that the intervention is cost effective and 94% probability that current practice is cost effective. This is repeated for a range of ceiling ratio values and plotted to form the CEAC.

Supplementary Material

Table 1. PubMed Search Hits

Search Terms	**Cost/resource/cost effective/cost utility**		**Cost effective/cost utility**		**Cost/resource**	
Search period	**1966-2016**	**% 2009-2016**	**1966-2016**	**% 2009-2016**	**1966 - 2016**	**% 2009-2016**
Glaucoma	1,032	50%	265	52%	1032	50%
Cataract	1,388	44%	281	45%	1,388	44%
Diabetic retinopathy	794	51%	245	44%	794	51%
Macular degeneration	754	64%	260	57%	754	64%
Glaucoma, Cataract, Diabetic Retinopathy and Macular degeneration	3,491	48%	945	48%	3,491	49%