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The value of evidence: a re-analysis of the use of steroids in head injury

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Abstract

Aims: Resources are not available to fund every healthcare intervention or research proposal. Formal analytical methods exist to inform decisions about which interventions to fund, how much to invest in changing clinical practice and whether further research is required to support these decisions. This study aims to present these formal methods in a non-technical way to make them accessible, and to demonstrate their value, to a wider audience.

Methods: A retrospective analysis was conducted assessing the use of steroids in brain injury. The benefits of steroids were uncertain, and use in practice highly variable, following a meta-analysis in 1997. On this basis the CRASH trial was designed and funding was obtained based on an informal assessment of the need for further research. Value of information methods are applied to demonstrate whether formal methods would have indicated the need for further research, and if so what data to collect. A cost-effectiveness analysis is used to demonstrate the value of reducing variability in practice and to explore how large a trial must be in order to change practice.

Results: The estimated cost of uncertainty before CRASH was high at 207 deaths, 5,508 healthy years, 3,542 net health benefits, or £71 million, indicating the need for further evidence on the use of steroids in head injury. A future trial should be designed to measure the proportion of patients left dead, vegetative, or severely disabled following traumatic brain injury.

Conclusions: Informal methods based on risk of death suggested the need for further research. Formal methods also demonstrated this need, and furthermore allow discrimination between competing research designs to evaluate the use of steroids, and research in other areas.

Introduction

In a budget-constrained healthcare system, resources are not available to fund every healthcare intervention or research proposal and so choices need to be made between competing alternative uses of resources. This results in an opportunity cost being incurred with each adoption or research decision, i.e. a particular deployment of resources in one particular area of health involves forgoing the benefits generated from alternative deployments of the same resources elsewhere. The challenge is to ensure that the benefits gained from implementing a treatment or research decision outweighs the benefits lost from what has to be sacrificed elsewhere in the healthcare system.

Formal analytic methods are commonly used to establish the cost-effectiveness of alternative healthcare interventions and programmes.[1] These methods enable efficiency-led decisions to be made about which intervention/technology should be adopted in practice given the existing evidence base and the uncertainty surrounding outcomes and resource use.[2 3] However, if the decision based on the best available evidence turns out to be wrong, there will be consequences in terms of health benefits and resources forgone.[4] A valuable extension to the decision problem is the need to establish whether additional evidence is required to support the adoption of a particular intervention in practice.[5]

Formal methods of value of information (VOI) analysis inform decision makers about the expected costs of uncertainty by considering the consequences of adopting a wrong treatment decision. They quantify the cost of uncertainty in terms of the loss in health benefits and resources in order to assess the extent to which gaining more evidence would result in a change in decision about the use of a technology.[4 6] Furthermore, these methods can be used to establish the maximum returns to investment in strategies to get treatment decisions implemented into clinical practice.[7]

Despite its potential to make better decisions about the use of research resources, formal VOI methods are not always used to make decisions about

research priorities and commissioning.[8] This is partly because those institutions with the remit for making adoption decisions are often separated from those responsible for prioritising and commissioning research, yet the decision to adopt a technology should not be separated from the question of whether more evidence is required to support the adoption decision.

Without formal methods of VOI analysis, a number of other approaches are used for setting research priorities. These include measures of the burden of the disease and technology[9 10], the expected payback from research[11-13], and the welfare losses due to variations in clinical practice.[14] In addition, when a number of research bids are placed for funding, the decision to fund a particular study is often dependent on the comparators in the portfolio of programmes requiring funding. Attempts to identify research priorities across broad clinical areas without a measure of the societal value of particular research can lead to mistaken priorities.[8]

This paper uses a case study to assess formal approaches of VOI analysis to inform policy decisions about research priorities. The case study relates to a high profile example of where additional research was required to prevent thousands of iatrogenic deaths. The study relates to the use of steroids for traumatic brain injury. The existing evidence base was insufficient to reliably determine whether or not there was a clinical benefit from the use of steroids following head injury.[15] The lack of reliable evidence led to large variations in the clinical use of steroids worldwide.[16-19] The decision uncertainty prompted the need to obtain additional evidence. An informal approach was taken which led to the funding of a large multicentre randomised control trial. The purpose of this study is to assess formal analytic approaches of VOI analysis by undertaking a retrospective analysis of the evidence base before the decision was taken to fund a large trial. We examine, through formal quantitative approaches, whether the pre-trial evidence informed the need to conduct a large trial. This study also aims to present these formal methods in a non-technical way to make them accessible to a wider audience.

Background

Worldwide millions of people die from head injury each year. The annual incidence of severe brain injury is estimated to be about 15 per 100,000 people.[20] In the UK, the incidence of severe brain injury is estimated to be around 9,000 per year. Therefore, the expected population who could potentially benefit from an effective treatment over 5 years is around 45,000. A systematic review was conducted in 1997 to examine the effectiveness of using steroids on death and disability following significant brain injury.[15] The review concluded that steroids may reduce death by 1-2% but it could be up to 6% lower or 2% higher mortality.[15] If steroids did reduce the risk of death by 2%, then treatment of 50,000 people would avoid 1,000 deaths. However, there is a risk that steroids could cause unnecessary deaths. The existing trials before the year 2000 were too small to demonstrate or refute the possibility of a moderate but clinically important benefit. Due to a lack of reliable evidence of the effects of steroids on brain injury, there was inconsistent use of steroids worldwide. A 1998 UK survey reported that steroids were used in 12% of cases of brain injury.[19] On this basis, over a period of 5 years, around 5,400 patients (12% of 45,000) would either benefit or be harmed from the use of steroids, while 39,600 patients would either be denied an effective treatment or be saved from the effects of a harmful one.

In 2000, an informal decision was made to conduct a large randomised control trial (CRASH) to examine the effects of steroids on head injury. A convincing case was put forward to the Medical Research Council (MRC) to fund this trial on the basis of five reasons: (1) Existing trials were too small to demonstrate or refute benefit; (2) there was evidence of benefit from steroids in spinal cord injury and it was expected that steroids would perform in a similar way in brain injury; (3) animal studies showed that steroids may reduce post-traumatic neuronal degeneration; (4) there was wide variation in the use of steroids within and between countries; and (5) a pilot phase of the CRASH trial confirmed the feasibility of a large scale trial. Based on these five reasons, the funding application was successful and the CRASH trial took place.

The CRASH trial randomised around 10,000 patients from multicenters worldwide to examine the effect of an early administration of a 48 hour infusion of corticosteroid (methylprednisolone) on the risk of death and disability after head injury.[21 22] The results of the trial were alarming. The relative risk of death at 6 months with steroids was 1.15, with a 95% confidence interval ranging from 1.07 to 1.24.[22] The results suggest that steroids kill head injury patients. Without this large trial, the continued use of steroids could be causing 5,400 iatrogenic deaths over a 5 year period in the UK.

Methods

Bayesian decision theory provides a formal analytic framework, which can be used to establish the value of acquiring additional information to inform a decision problem.[23 24] We assess whether formal approaches of VOI analysis could have aided decisions about steroid use for head injury by quantifying:

1. Whether there should have been widespread adoption or rejection of steroids in practice given the evidence that existed prior to the CRASH trial.
2. What value would have been placed on obtaining further evidence to inform that decision prior to the CRASH trial?
3. What value would have been placed on implementation strategies to reduce variation in clinical practice prior to the CRASH trial?

We demonstrate whether these formal approaches would have indicated the need for further research and the need to conduct CRASH.

The application of VOI analysis requires 5 tasks to be completed[6]: (1) The synthesis of clinical evidence on the effects of steroids on traumatic brain injury; (2) construction of a decision analytic model to represent the clinical decision problem; (3) a probabilistic analysis of the model to characterise the uncertainty in the decision; (4) an estimate of the value of additional information through research to reduce the uncertainty and inform the decision; and (5) an estimate of the value of strategies required to reduce variation in clinical practice.

Details of the structure of the decision model, sources of evidence, methods of synthesis and the conduct of the probabilistic and VOI methods are to be reported elsewhere.

Results

Clinical evidence and the cost of uncertainty

There are 19 randomised control trials comparing the use of steroids to not using steroids in the treatment of traumatic brain injury before the CRASH trial.[15 25] The primary outcome reported across the trials is mortality at a mean follow-up time of 6 months. A secondary outcome reported is the Glasgow Outcome Scale (GOS), which categorises patients into one of 5 possible health states: (1) Dead, (2) vegetative, (3) severely disabled, (4) moderately disabled, and (5) good recovery. A Bayesian random effects meta-analysis was used to synthesise the evidence in relation to these outcomes.[26]

The point estimate of the odds ratio for death, when providing steroids, was 0.93. Thus, the evidence suggested that on average the use of steroids could reduce the proportion of patients dying from traumatic brain injury by 2%. However, this evidence was subject to considerable uncertainty. The 95% credible interval (Bayesian analogue of the 95% confidence interval) for the odds ratio ranged from 0.71 to 1.18, indicating that the change in percentage of deaths with steroids could lie between -8% and +4%. If steroids did reduce the risk of death by 2%, then treatment of 50,000 patients would avoid 1,000 deaths. However, if steroids increased the risk of death by 4%, then treatment of 50,000 patients would cause 2,000 excess deaths.

Given that over a period of five years approximately 45,000 patients in the UK are eligible for treatment with steroids, Figure 1 shows the impact of the uncertainty in the effect of steroids in terms of the numbers of deaths over five years.

>>Figure 1 about here<<

Although steroids are expected to be life-saving on average, the uncertainty is such that the probability that providing steroids could cause excess deaths is

26%. This level of error probability is unlikely to be acceptable to many clinicians, who may require stronger evidence to support the use of steroids. In clinical trials, a statistical significance level of 5% is used as a hurdle to regarding one treatment as superior to another. On this basis, steroids would not be regarded as superior to no steroids. However, steroids were used in clinical practice by an estimated 12% of centres in 1998, showing that the decision to utilise steroids was not based solely on a statistically significant demonstration of benefit.

Gathering additional evidence to inform the use or abandonment of steroids would be expected to reduce the probability of making a wrong treatment decision. In the limit, if clinicians knew exactly the effect of steroids in comparison to no steroids, they would only choose to provide steroids when they were life-saving. Figure 2 illustrates the difference between taking the decision to use steroids when the odds ratio for death is uncertain and taking that same decision when the odds ratio is known with certainty. The difference in the number of deaths expected represents the cost of uncertainty. Based on the best judgement of current evidence, you would choose to give steroids to head injury patients (Figure 2a) since 818 (16,108-15,290) fewer deaths are expected on average than not using steroids. If we could reduce all the uncertainty in this decision, i.e. remove the 26% error probability (Figure 2b) by acquiring further evidence, we could save an estimated 207 (15,290-15,083) lives over the course of five years. In other words, if our decision based on the best available evidence turns out to be wrong, the implication is the loss of a maximum of 207 lives.

>>Figure 2 about here<<

Length and quality of life after the use of steroids

The health impacts of traumatic brain injury are not described solely in terms of number of deaths. Those patients that survive suffer further health consequences in terms of disability and reduction in length and quality of life. The magnitude of these health impacts may also be affected by steroid use. A proportion of the published trials described the outcomes of patients in

terms of the GOS. Table 1 shows the proportion of patients expected to be in each health state according to steroid use, and the quality-adjusted life expectancy for a 50 year old patient in these health states.

Table 1. Distribution of outcomes and quality adjusted life expectancy according to Glasgow Outcome Scale.

Glasgow Outcome Scale	Steroids	No steroids	Quality adjusted life expectancy
Dead	0.335	0.353	0
Vegetative	0.048	0.038	0.56
Severe disability	0.135	0.107	3.24
Moderate disability	0.116	0.121	10.51
Fully recovered	0.365	0.380	15.39

Quality adjusted life expectancy describes the remaining life expectancy in terms of years of full health

The evidence synthesis of trials reporting the composite endpoint of dead, vegetative or severely disabled indicated that the use of steroids increased the risk of being in this category, with an odds ratio of 1.10 (95% CrI 0.81 to 1.53). Thus, although steroids were expected to reduce the number of deaths on average, those surviving were more likely to be in a worse health state. The uncertainty in the effect of steroids as measured by this composite endpoint is greater than the uncertainty around the effect on death as fewer trials describe the composite outcome of survivors.

The proportion of patients left dead, vegetative or severely disabled with steroids was estimated to be 2% greater than with no steroids (95% CrI -5% to 10%). This increase in negative outcomes (proportion left vegetative or severe) must be compared with the improvement in number of deaths in order to come to some overall assessment about the health impacts of steroid use. Evidence regarding the life expectancy and the health related quality of life of patients in each of these health states allows quality-adjusted life expectancy to be estimated. This quantifies, in terms of equivalent additional years of full health, the benefit of being in one of the better health states for survivors of

traumatic brain injury. Figure 3 shows the distribution of outcomes if the decision about whether to use steroids is based on the number of years lived in full health, rather than number of deaths.

>>Figure 3 about here<<

The use of steroids is expected, on average, to reduce the number of healthy years lived. Thus, when length and quality of life are considered in addition to numbers of deaths, steroids no longer appear to offer a small benefit and instead appear to be harmful. The probability that steroids reduced the number of healthy years lived is 63%. If the decision were made to not provide steroids on this evidence, it would again be subject to uncertainty, with 8,481 more healthy years expected on average but this could range from -35,853 to 58,345. The cost of the uncertainty, which encompasses the probability of a wrong decision and the number of healthy years forgone when a wrong decision is made, is estimated to be 5,508 healthy years.

Costs

Considering the decision to use steroids in terms of their clinical benefit or harm to patients who receive them does not fully represent the impact of their use or non-use on the healthcare system as a whole. Over a 5 year period, approximately 45,000 people with severe brain injury in the UK will be affected by the decision on whether to use steroids or not. However, many other patients in the UK without brain injury will also be affected by this decision. This is because the deployment of resources in one particular area of health such as brain injury involves forgoing the benefits generated from alternative deployments of the same resources, i.e. funding, elsewhere. By combining information about the healthcare resources required by patients in each health state, and the costs of providing steroids themselves, it is possible to calculate the total expected costs of patients with traumatic brain injury, with or without steroids. Table 2 shows the expected health outcomes and costs for patients with traumatic brain injury.

Table 2. Health outcomes and costs expected for a patient with traumatic brain injury according to steroid use and Glasgow Outcome Scale

	Steroids		No steroids	
	Healthy years	Costs	Healthy years	Costs
Dead	0	0	0	0
Vegetative	0.03	£15,615	0.02	£12,405
Severe disability	0.44	£91,610	0.35	£72,735
Moderate disability	1.22	£16,937	1.27	£17,625
Fully recovered	5.62	£7,136	5.85	£7,428

Providing steroids to patients with traumatic brain injury is expected to increase the number of patients left severely disabled. This carries health dis-benefits for the patients themselves, but also places a higher demand on healthcare resources, displacing a greater amount of health-generating activities elsewhere. By estimating the amount of health that could be generated by the healthcare resources required to fund steroid use, it is possible to quantify the amount of health forgone by transferring resources from elsewhere in the healthcare system to the provision of steroids. The National Institute for Health and Clinical Excellence (NICE) in the UK regards interventions with a cost per quality-adjusted life year gained less than £20,000 as cost-effective, suggesting that each £20,000 worth of healthcare resources can be used to generate one additional healthy year with existing healthcare activities. Table 3 shows the total costs and healthy years for patients with traumatic brain injury with and without steroids, and by converting costs to health forgone at a rate of £20,000 per healthy year, the net health benefits.

Table 3. Total expected costs, quality-adjusted life years and net health benefits for a patient with traumatic brain injury, with and without steroids

	Steroids	No steroids	Difference
Costs	131,374	110,193	21,181
QALYs	7.30	7.49	-0.19
Net health benefits = QALYs – Costs/£20k	0.73	1.98	-1.25

Giving steroids to a patient when it is more cost-effective not to give them uses up approximately £21,000 of NHS resources, which is equivalent to a loss of just over one year of full health. Figure 4 shows the distribution of health outcomes in terms of net health benefits if the decision is made to provide steroids to all patients with brain injury over the next five years.

>>Figure 4 about here<<

The decision to use steroids is expected, on average, to reduce the number of net health benefits by -53,000, although this is subject to uncertainty and could range from -180,000 to +43,600. The probability that steroids reduce the number of net health benefits is 85%. The uncertainty in the clinical endpoints has been propagated into uncertainty surrounding costs and effects. By considering the health forgone elsewhere in the healthcare system if resources are transferred to the provision of steroids and the follow-up care of those survivors left in a worse health state, steroids appear less attractive. The evidence suggests that the use of steroids is not cost-effective. However, if this recommendation is made and it turns out to be wrong, some patients will have been denied an effective treatment or have been saved from the effects of a harmful one. The cost of uncertainty is determined jointly by the probability that our decision was wrong and the consequences of that wrong decision. It is the difference between the net health benefit we could have gained by making the right decision and the net health benefit based on the

current evidence. The cost of uncertainty is estimated to be 3,542 units of net health benefits. This is equivalent to £71 million (3,542*£20,000). This represents the maximum amount that the healthcare system should be willing to pay for the additional evidence to inform the decision on the use of steroids for head injury.

Sources of uncertainty

The sources of uncertainty in the decision to provide steroids to patients with traumatic brain injury include uncertainty in the efficacy of steroids (i.e. the risk of death and the risk of being left in a vegetative or severely disabled health state), uncertainty in the quality and length of life of survivors and uncertainty in the amount of healthcare resources required to treat patients with head injury. The cost of uncertainty discussed above relates to the combined impact of these on the overall decision uncertainty. However, we can separate apart the sources of uncertainty to determine which element(s) contribute most to the decision uncertainty in order to indicate where more evidence is most valuable.

Figure 5 shows the cost of uncertainty associated with each element of the decision relative to the overall decision uncertainty.

>>Figure 5 about here<<

It is clear that uncertainty in the risk of death and the risk of being left in a vegetative or severely disabled health state is almost exclusively responsible for the overall decision uncertainty. It is noteworthy that a future trial which reports simply the number of deaths in each arm would not reduce the decision uncertainty, and this is because it would not provide information on the length and quality of life of the survivors, which is crucial to the decision on whether to provide steroids or not. In addition, once the proportion of patients who are left dead, vegetative or severely disabled is known, there is no additional value in knowing more precisely their outcome in terms of the Glasgow Outcome Scale. This would indicate that a future trial should be designed to compare the provision of steroids with usual care that measures

the proportion of patients left dead, vegetative or severely disabled following traumatic brain injury.

Level of implementation

The cost of uncertainty represents the maximum value of further research as it describes the expected gain in health outcomes if the decision to use steroids can be made in the absence of uncertainty. The actual value from further research will be determined by the amount by which uncertainty is reduced, but also by its affect on practice. If there is variation in practice, with some clinicians not implementing the treatment option which is expected to provide the greatest benefits, any benefits from further research will not be fully realised. Before the CRASH trial, about 12% of patients received steroids following head injury. Based on the best judgement of the current evidence, the expected net health gain for those patients was 0.73 units (Table 3), whereas the expected gain for the 88% of patients not receiving steroids was 1.98 units. Convincing the 12% of clinicians that are using steroids to stop using them would be expected to increase the net health benefits by approximately 6,750 (1.25*45,000*0.12) over 5 years. However, the benefit from investing in changing clinical practice would be uncertain, and could range from -5,244 to 21,580 net health benefits given that the decision about which treatment represents best practice was highly uncertain.

Designing a future trial

If formal methods of VOI analysis were applied to the evidence base before the CRASH trial, we would conclude that there was a high value to further research to reduce the uncertainty in the decision on whether to use steroids or not. The cost of uncertainty was estimated to be high, at 207 deaths, 5,508 healthy years, 3,542 net health benefits, or £71 million.

The CRASH trial itself was estimated to cost £2 million, which, if invested elsewhere in the healthcare system, might have generated 2million/20,000=100 healthy years. In addition, the CRASH trial recruited 10,008 patients, 5,007 of whom were randomised to receive steroids, potentially forgoing 932 healthy years as a result of receiving an inferior

treatment. Combining the cost of the research with the opportunity costs to patients included in the trial, the total cost of the CRASH trial can be estimated as 1,032 healthy years. The benefits of CRASH were two-fold, reducing uncertainty in the efficacy of steroids to below the 5% significance level normally applied in clinical trials, and changing clinical practice. The benefits of CRASH are therefore likely to compare favourably with the resources invested in generating the additional information.

A trial that recruited 10,000 patients would be expected to reduce the cost of uncertainty by 93%. Reducing uncertainty by that amount would imply a benefit of 5,136 healthy years or 3,303 net health benefits over five years of treating patients for traumatic brain injury. However, the full benefits of the reduction in the decision uncertainty are only gained if the additional information also changes the treatment decisions made by clinicians.

Discussion

The present study set out to perform a retrospective analysis of a policy-relevant decision in order to assess formal methods of VOI analysis. The case study, relating to the use of steroids for traumatic brain injury, demonstrated that standard methods of VOI analysis can provide informative results about whether more evidence is required to support the adoption of an intervention and the type of evidence required. These formal methods quantify the uncertainty in the clinical decision and provide an explicit value of investing in a particular programme of research. In turn, they provide a measure of the societal value of particular research, which can be used to identify research priorities across a broad range of clinical areas.

Although formal approaches of VOI analysis provide the necessary tools for prioritorising research funding, the decisions often made by panels and commissioning boards are based on informal methods, e.g. subjective scoring systems. This may in part be due to unfamiliarity with cost-effectiveness analysis and decision modelling, leading to a reluctance to accept and base decisions on unfamiliar methods.[8] There needs to be a drive towards explaining these methods in a non-technical way to a wider audience,

particularly to those responsible for research prioritorisation and commissioning. By increasing the transparency and explicitness of the methods used, research and development committees will benefit from the measure of the societal value of a particular research programme or study. Achieving this may be crucial in many cases as the opportunity cost of adopting an intervention without considering whether more evidence is required is the value of information which may be forgone. In the case of steroids for traumatic brain injury, it was pertinent that further research in the form of a trial took place in order to save thousands of iatrogenic deaths.

References

1. Sculpher M, Claxton K, Akehurst R. 'It's just evaluation for decision making: recent developments in, and challenges for, cost-effectiveness research'. In: Smith PC, Ginnelly L, Sculpher M, editors. *Health policy and economics. Opportunities and challenges.* Maidenhead: Open University Press, 2005.
2. Briggs A, Claxton K, Sculpher M. *Decision modelling for health economic evaluation*. Oxford: Oxford University Press, 2006.
3. Drummond MF, Sculpher MJ, Torrance GW, O'Brien B, Stoddart GL. *Methods for the economic evaluation of health care programmes*. Oxford: Oxford University Press, 2005.
4. Claxton K. The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies. *Journal of Health Economics* 1999;18:341-64.
5. Claxton K, Posnett J. An economic approach to clinical trial design and research priority-setting. *Health Economics* 1996;5:513-24.
6. Claxton K, Ginnelly L, Sculpher MJ, Philips Z, Palmer S. A pilot study on the use of decision theory and value of information analysis as part of the NHS Health Technology Assessment programme. *Health Technology Assessment* 2004;8(31):1-103.
7. Fenwick E, Claxton K, Sculpher M. The value of implementation and the value of information: combined and uneven development. *Centre for Health Economics. University of York* 2005;CHE research paper 5.
8. Claxton KP, Sculpher MJ. Using value of information analysis to prioritise health research. Some lessons from recent UK experience. *Pharmacoeconomics* 2006;24(11):1055-68.
9. Gross CP, Anderson GF, Powe NR. The relation between funding by the National Institutes of Health and the burden of disease. *New England Journal of Medicine* 1999;340:1881-7.
10. Michaud CM, Murray CJ, Bloom BR. Burden of disease: implications for future research. *Journal of the American Medical Association* 2001;285(5):535-9.
11. Buxton M, Hanney S. Assessing payback from Department of Health Research and Development: second report. HERG Research Report 24. *Uxbridge: Brunel University* 1997.

12. Davies L, Drummond MF, Papanikolaou P. Prioritizing investments in health technology assessment. *International Journal of Technology Assessment in Health Care* 2000;16:73-91.
13. Townsend J, Buxton M. Cost-effectiveness scenario analysis for a proposed trial of hormone replacement therapy. *Health Policy* 1997;39:181-94.
14. Phelps CE, Parente ST. Priority setting in medical technology and medical practice assessment. *Medical Care* 1990;28(8):703-23.
15. Alderson P, Roberts I. Corticosteroids in acute traumatic brain injury: systematic review of randomised controlled trials. *British Medical Journal* 1997;314:1855-59.
16. Ghajar J, Hariri RJ, Narayan RK, Iacono LA, Firlik K, Patterson RH. Survey of critical care management of comatose, head-injured patients in the United States. *Critical Care Medicine* 1995;23:560-7.
17. Jeevaratnam DR, Menon DK. Survey of intensive care of severely head injured patients in the United Kingdom *British Medical Journal* 1996;312:944-947
18. Matta B, Menon D. Severe head injury in the United Kingdom and Ireland: A survey of practice and implications for management. *Critical Care Medicine* 1996;24:1743-1748.
19. McKeating EG, Andrews PJ, Tocher JI, Menon DK. The intensive care of severe head injury: a survey of non-neurosurgical centres in the United Kingdom. *British Journal of Neurosurgery* 1998;12(1):7-14.
20. Sauerland S, Maegele M. A CRASH landing in severe head injury. *The Lancet* 2004;364:1291-92.
21. CRASH trial collaborators. Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. *The Lancet* 2004;364:1321-28.
22. Edwards P, Arango M, Balica L, et al, CRASH trial collaborators. Final results of MRC CRASH, a randomised placebo-controlled trial of intravenous corticosteroid in adults with head injury - outcomes at 6 months. *The Lancet* 2005;365(9475):1957-9.
23. Pratt J, Raiffa H, Schlaifer R. *Statistical decision theory*: Cambridge: MIT Press, 1995.
24. Raiffa H, Schlaifer R. *Probability and statistics for business decisions*: New York: McGraw-Hill, 1959.
25. Alderson P, Roberts I. *Corticosteroids for acute traumatic brain injury (Cochrane Review)*. Oxford: Update Software: The Cochrane Library, 1999.
26. Smith TC, Spiegelhalter DJ, Thomas A. Bayesian approaches to random-effects meta-analysis: a comparative study. *Statistics in Medicine* 1995;14(24):2685-99.

Figure 1. Distribution of number of deaths expected over five years if steroids are provided to patients with traumatic brain injury

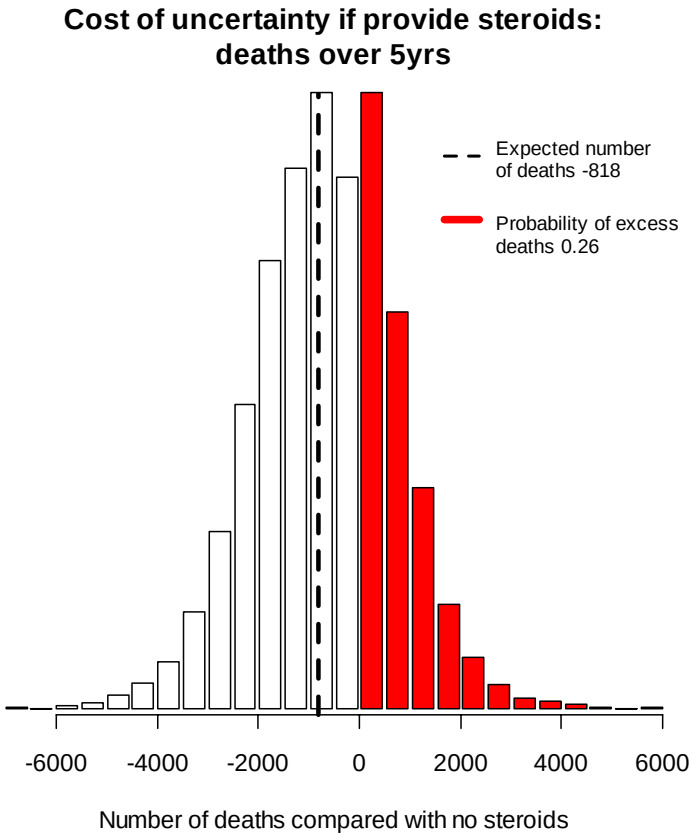

Figure 3. Distribution of healthy years lived if steroids are provided to all patients with traumatic brain injury over next five years

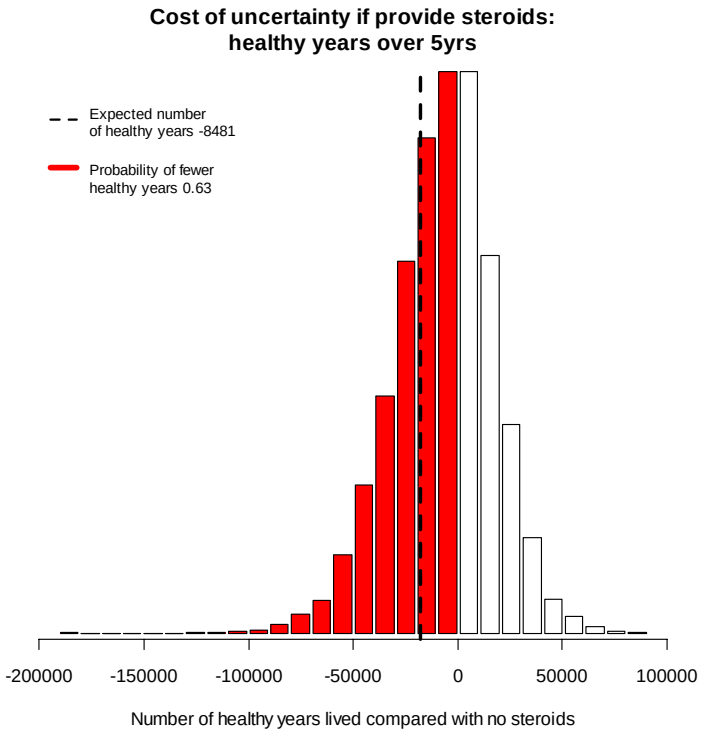

Figure 2. Expected number of deaths when the decision to used steroids is based on (a) uncertain information regarding the odds ratio for death with steroids; (b) perfect knowledge of the odds ratio for death with steroids.

Figure 4. Distribution of net health benefits if steroids are provided to all patients with traumatic brain injury over next five years

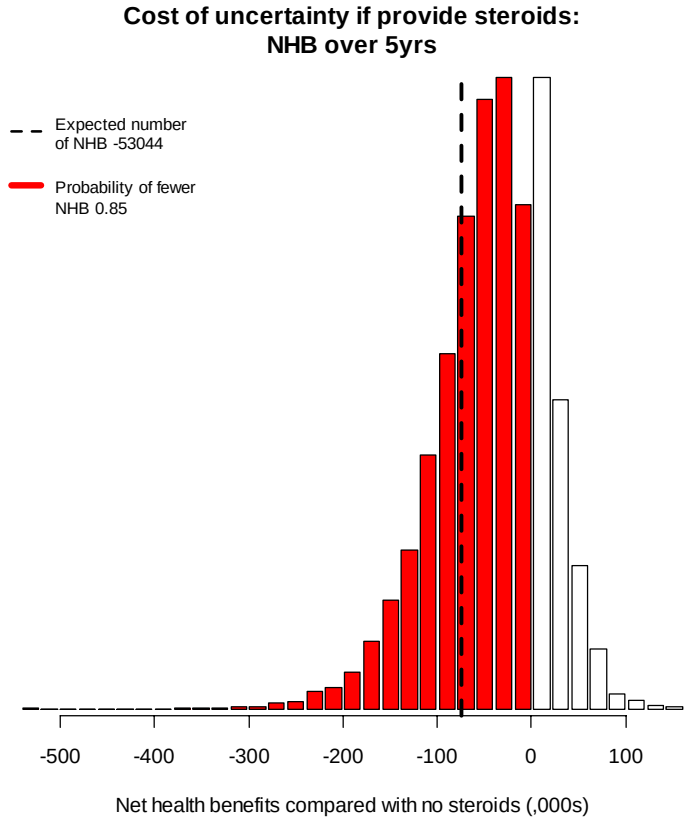

Figure 5. The cost of uncertainty for each element of the decision problem