ELSEVIER

Journal of Clinical Epidemiology 65 (2012) 863–868

Journal of Clinical Epidemiology

The ‘‘Lost NNT’’ can be used to represent uncertainty surrounding number needed to treat

Mohsen Sadatsafavi[a,b,*], Saeedreza Ganjizadeh[c], Rose Hatala[c], Carlo Marra[a], Mark FitzGerald[b,c]

[a]*Collaboration for Outcomes Research and Evaluation, Faculty of Pharmaceutical Sciences, University of British Columbia, 2146 East Mall, Vancouver, BC, Canada V6T 1Z3*

[b]*Centre for Clinical Epidemiology and Evaluation, Vancouver Coastal Health Institute, 828 West 10th Avenue, Vancouver, BC, Canada V5Z 1M9*

[c]*Department of Medicine, University of British Columbia, 2775 Laurel Street, Vancouver, BC, Canada V5Z 1M9*

Accepted 2 January 2012; Published online 30 May 2012

Abstract

Objectives: The uncertainty around number needed to treat (NNT) is often represented through a confidence interval (CI). However, it is not clear how the CI can help inform treatment decisions. We developed decision-theoretic measures of uncertainty for the NNT.

Study Design and Setting: We build our argument on the basis that a risk-neutral decision maker should always choose the treatment with the highest expected benefit, regardless of uncertainty. From this perspective, uncertainty can be seen as a source of ‘‘opportunity loss’’ owing to its associated chance of choosing the suboptimal treatment. Motivated from the concept of the expected value of perfect information (EVPI) in decision analysis, we quantify such opportunity loss and propose novel measures of uncertainty around the NNT: the Lost NNT and the Lost Opportunity Index (LOI).

Results: The Lost NNT is the quantification of the lost opportunity expressed on the same scale as the NNT. The LOI is a scale-free measure quantifying the loss in terms of the relative efficacy of treatment. We illustrate the method using a sample of published NNT values.

Conclusion: Decision-theoretic concepts have the potential to be applied in this context to provide measures of uncertainty that can have relevant implications.

Keywords: Number needed to treat; Value of information; Uncertainty; Bayesian statistics; Decision analysis; Confidence interval

1. Introduction

When deciding between two or more treatment options, decision makers (clinicians, patients, and policy makers) need to know the relative efficacy of treatments for the outcome of interest. There are several statistics to measure relative efficacy. Among them, the number needed to treat (NNT), that is, the number of patients who must be treated to achieve one favorable outcome (or to avoid one adverse outcome), is one of the most widely reported in medical decision-making literature [1]. The NNT, calculated as the reciprocal of the absolute risk reduction (ARR), was originally proposed by Laupacis et al. [2] as a measure for presenting the results of clinical trials with binary outcomes. It has since been extended for use with continuous outcomes [3] and survival data [4], and has led to closely related measures, such as the number needed to harm [5], number needed to screen [6], and the number needed to vaccinate [7].

In general, the NNT can be interpreted as quantifying the extra ‘‘effort’’ associated with the alternative treatment to achieve one outcome of interest. In Laupacis’ words, ‘‘it tells clinicians and patients in more concrete terms how much effort they must expend to prevent one event’’ [2]. When the options in front of the decision maker are treatment vs. no treatment, the NNT helps illustrate that the treatment is costly and has potential adverse effects. When the NNT is being calculated for an alternative vs. a standard treatment, this is often because the alternative treatment is more effective but also more expensive and/or associated with a higher rate of adverse effects. In the context of the NNT, the term ‘‘effort’’ is loosely defined but can point to the time, labor, monetary costs, and patient risk that accompany any treatment.

Although Laupacis’ definition of the NNT considers the treatment decision made by clinicians and patients, the NNT can equally be used in health policy decision making

* Corresponding author. Tel.: +1 604-822-9460; fax: 604-875-5179.
E-mail address: msafavi@mail.ubc.ca (M. Sadatsafavi).

0895-4356/$ - see front matter
doi: 10.1016/j.jclinepi.2012.01.022

What is new?

Key finding

Currently, confidence interval is the standard way of communicating uncertainty around the number needed to treat (NNT). But the CI is not directly relevant to the treatment decision.

Uncertainty around treatment only matters because it may result in the choice of suboptimal treatment and hence causing an opportunity loss.

What this adds to what was known?

This article applies the principles of value of information analysis to the NNT context and provides two related measure of uncertainty: the Lost NNT and the Lost Opportunity Index (LOI).

What is the implication, what should change now?

Decision-analytic concepts can be applied to the NNT to provide measures of uncertainty that are more relevant to decision-making task than generic statistical measures of uncertainty like the CI.

The Lost NNT and LOI are especially applicable to population-level policy making on the adoption of competing treatment as they can help quantify the areas of greatest need for the investment of research fund

when the impact of decision at the population level (e.g., endorsing the coverage of a particular medication vs. another) is concerned [17]. For example, Heller et al. [8] proposed dividing the NNT by the proportion of the diseased population eligible for the intervention (disease impact number) and further by the proportion of the population with the disease of interest (population impact number) to provide a population perspective to the NNT [8,9].

One of the ways to use the NNT in making treatment decisions is to compare its value against a threshold NNT (NNT_T) [10], the point at which the effort and benefits are considered equal. In some situations, the choice of the NNT_T is obvious. For example, if treatments being compared differ only in their efficacy and are equal in all other respects, then the optimal treatment is the one that has the highest efficacy; in this case $NNT_T = \infty$ corresponding to ARR_T (treatment threshold on the ARR) of 0. In more complex situations, the NNT_T can be explicitly derived from the benefits, risks, and monetary costs associated with each treatment, and there are published methods on its calculation [11]. Even if such an objective threshold is not used, it has been argued that at the time of the decision, the NNT is being implicitly compared with an internal threshold based on subjective understanding of the risks, benefits, and preferences [12].

Furthermore, the NNT, like other indices estimated from sample data, is accompanied by sampling uncertainty. It is recommended that studies reporting NNTs always report confidence intervals (CI) as well [13]. Unfortunately, the NNT, as a reciprocal of the ARR, has some statistical disadvantages for calculating the CI when the ARR's CI crosses zero. In this situation, the bounds on the CI define an interval that contains infinity; these bounds therefore represent both the NNT and number needed to harm, and hence the CI does not have an intuitive interpretation [13,14].

2. The relevance of uncertainty in the NNT: the chance and consequences of making a wrong decision

The CI around the NNT communicates information about the degree of uncertainty around the value of the NNT, caused by the finite sample of the original studies reporting the ARR and the NNT. However, the question remains as to the practical relevance of such sampling uncertainty in medical decision making. It might be proposed that if the CI around the NNT contains the threshold NNT, the hypothesis that the alternative treatment is superior to the standard treatment is statistically rejected. Hence, the standard treatment remains the best option. But such hypothesis testing is inherently arbitrary (after all, why significance at the 5% level and not, say, 10%?) and is not necessarily in line with making the best treatment decision. (What if the underlying study was simply underpowered to detect a positive NNT?)

From a decision-theoretic viewpoint, the best treatment is the one that has the highest ''expected'' benefit [15]. An NNT that is below the NNT_T means the expected value of the efficacy of the alternative treatment is above the treatment threshold and hence is the treatment of choice, regardless of the statistical significance of difference between the NNT and the NNT_T or the CI around the NNT. Likewise, if the NNT is above the NNT_T, the standard treatment has the highest expected benefit and should be the treatment of choice. That is, it is the comparison between the point estimate of the NNT and the NNT_T that should influence the treatment decision, and statistical inference around the NNT is irrelevant for optimal decision making [15]. A decision maker who decides on the choice of treatment by comparing the NNT with the NNT_T will achieve the highest number of favorable outcomes per treatment decisions in the long run [15]. Following this argument, we developed indices that quantify and communicate such opportunity loss for the NNT.

3. The Lost NNT

The concept of the Lost NNT is analogous to the expected value of perfect information in health economics, which quantifies the opportunity loss because of not having perfect information in making a decision [16]. The calculation is

the quantification of the following line of reasoning: had we known the true value of treatment efficacy, we would have avoided choosing the alternative treatment if its efficacy (in terms of the ARR) was below our treatment threshold and would have adopted the standard treatment instead. Likewise, we would have adopted the alternative treatment if the true treatment efficacy was above the treatment threshold. We do not know the true value of treatment efficacy, but we can apply this algorithm to all its likely values and average the results. Note that first, the above line of reasoning is strictly Bayesian, as the unknown ARR is treated as a random quantity whose true value is unknown but can be inferred from the data. Second, the calculations must be done on the ARR scale, not on the NNT scale. This is because the point estimate of the NNT is the reciprocal of the expected value of the ARR, not the expected value of the reciprocal of the ARR (an analogy between the NNT and the incremental cost-effectiveness ratio is established in the Appendix [see appendix on the journal's Web site at www.jclinepi.com], following which a decision-theoretic argument outlined in [17] can be applied to justify such an interpretation of the NNT).

The process conceptualized above can be formalized as follows: let μ indicate the true ARR and μ_T correspond to the threshold ARR. The expected benefit under current information, denoted by B_c, is:

$$B_c = \max[0,\ \mathrm{E}_\mu(\mu - \mu_T)] \tag{1}$$

Likewise, the expected benefit under perfect information, denoted by B_p, is:

$$B_p = \mathrm{E}_\mu[\max(0, \mu - \mu_T)] \tag{2}$$

The term E_μ means expectation with respect to the distribution of the ARR.

The difference between B_p and B_c is the opportunity loss owing to uncertainty, defined in terms of the probability of achieving the favorable outcome. This difference is on the ARR scale. As treatment efficacy is expressed as the NNT, the interpretation of such opportunity loss is the most intuitive if it too can be expressed in the same metric. We transform this back to the NNT scale and call this the Lost NNT, calculated as:

$$\mathrm{NNT}_{\mathrm{Lost}} = \frac{1}{B_p - B_c} \tag{3}$$

A Lost NNT of X can be interpreted in this way: for every X treatment decisions made between the alternative and standard treatments under current information, we, on average, miss one favorable outcome because of our uncertainty around the NNT.

Note that with no uncertainty around the NNT, there is no lost opportunity and the Lost NNT will be infinite. On the other hand, the wider the distribution of the NNT, the smaller the Lost NNT will be, reflecting the higher efficacy of the decision under perfect information compared with the decision under current information.

Another way to express this lost opportunity is in terms of the relative loss of treatment efficacy. We call this the Lost Opportunity Index (LOI):

$$\mathrm{LOI} = \frac{\mathrm{NNT}}{\mathrm{NNT}_{\mathrm{Lost}}} \tag{4}$$

The LOI thus shows the relative loss in treatment efficacy as a result of uncertainty. As an example, imagine the NNT is 10 and the Lost NNT is 50, corresponding to an LOI of 20%. Currently, for every 100 treatment decisions, we expect 10 more favorable outcomes using the alternative treatment. A LOI of 20% means we would have $10 \times 0.2 = 2$ more favorable outcomes per 100 treatment decisions with perfect information.

4. Analytical solutions and numerical methods for calculation of Lost NNT and LOI

If our current knowledge of the true ARR can be approximated by a normal distribution, then B_p can be calculated using the following equation (derivations provided in the Appendix, see appendix on the journal's Web site at www.jclinepi.com).

$$B_p = \sigma.\varphi\left(\frac{\mu_{\mathrm{T}} - \mu}{\sigma}\right) + (\mu - \mu_{\mathrm{T}}).\Phi\left(\frac{\mu - \mu_{\mathrm{T}}}{\sigma}\right) \tag{5}$$

where φ and Φ are the probability density and cumulative density functions of the standard normal distribution, respectively. The parameter σ is the standard deviation of the distribution of the ARR, which can often be estimated from the two-by-two tables of treatment vs. outcome or recovered from the ARR (or the NNT) and its standard error (SE) or CI, provided that these are based on an assumption of the normality of a sample distribution of the ARR. This is the case with the popular Wald-type CI for the ARR and NNT [19]. However, if the underlying sample from which the ARR and NNT are estimated is small, or if the ARR is close to -1 or 1, then other methods for presenting the CI bounds for the ARR are recommended [18,20–22], from which σ cannot readily be estimated. If there is any doubt about the appropriateness of the normality assumption for the ARR, one can use Monte Carlo simulation methods for the calculations, instead of using the abovementioned equation [23]. This is performed by randomly generating samples from the distribution of the ARR, calculating B_p, and repeating these calculations several times and averaging the results.

A spreadsheet facilitating the analytical and numerical methods for the calculation of the LOI and the NNT with instructions is available from http://www.core.ubc.ca/~msafavi/nnt/

5. Default decision thresholds for the NNT

If the decision maker's goal is to maximize treatment efficacy regardless of costs and possible harm (e.g., if adverse events are rare or are known to be equal for two treatments, and cost is equal between treatments or is not important for the decision maker), the NNT_T will be infinite (corresponding to $ARR_T = 0$). On the other hand, maximum uncertainty in treatment decisions happens when the observed and threshold NNTs are equal, hence the decision maker is indifferent toward treatment choice with the current information available. Therefore, by setting $NNT_T = NNT$, one can obtain a lower bound for the Lost NNT and an upper bound for the LOI. In the absence of a rigorously driven NNT_T, these two bounds on the LOI can be reported as an interval for the Lost NNT and the LOI for a range of plausible values of the NNT_T.

6. Examples from the literature

Table 1 presents the results of selected samples of NNTs taken from the publication of Altman [13] on the interpretation of CIs alongside the NNT. The NNTs are for 11 medications (different in type or dosage) for the treatment of postoperative nausea in children. We calculated the Lost NNT and the LOI with two treatment thresholds, $NNT_T = \infty$ (maximizing treatment efficacy) and $NNT_T = NNT$ (maximizing the impact of uncertainty), as described previously. All calculations are performed by recovering the ARR and its SE from the NNT and its CI bounds. Calculating the ARR and SE directly from the two-by-two tables, reported by Tramèr et al. [24], led to very similar results.

When $NNT_T = \infty$, the LOI varies from 0% for 5 of the medications to 73.9% for atropine 10. For all instances of zero LOI, the CI around the NNT is narrow and is entirely on the NNT-benefit (positive) side, conforming to the intuition that there is not much doubt about the benefit of treatment in such situations. The LOI is high for atropine 10 because the CI is wide and the NNT_T is almost in the middle of the CI (for $NNT_T = \infty$, a CI contains NNT_T when it covers both the NNT-harm and NNT-benefit ranges). Also, there is a clear dose–response relation for the NNTs of droperidol. This is generally followed by an increasing Lost NNT and a declining LOI, with an exception. As the uncertainty for droperidol 50 is higher than that of droperidol 20, the opportunity loss is higher despite a higher point estimate of efficacy. This demonstrates the combined effect of the point estimate and the width of the CI around the NNT on the opportunity loss. When $NNT_T = NNT$, the lost opportunity is at its maximum value, therefore all Lost NNTs are lower and LOIs are higher in the second column than in the first column.

An example of the application of the Lost NNT and LOI at the policy level is provided in the Appendix (see appendix on the journal's Web site at www.jclinepi.com).

7. Comments

Evidence-based medicine seeks to support medical decision making with objective methods to maximize outcomes. The emphasis on using measures, such as the NNT, to inform treatment decisions is an attempt toward such objectivity, yet the inevitable uncertainty surrounding NNT values influences objective decision making in a way that has not heretofore been quantified. To show the practical importance of uncertainty surrounding the NNT in making treatment decisions, we introduced the Lost NNT and the LOI as measures that explicitly quantify opportunity loss owing to lack of information. The Lost NNT and the LOI are linked to the measures of opportunity loss derived from the expected value of information analysis in health economics [15,25]. The LOI can be reported in percent and can be easily interpreted in terms of the loss of efficacy of treatment owing to our lack of perfect knowledge about its value and the resulting chance of making the suboptimal treatment choice. Similar concepts can be developed for other measures of treatment efficacy, such as odds ratio, relative risk, and so on. Such measures are, however, mainly epidemiological indices aimed at communicating the treatment effect size, whereas the NNT specifically informs the

Table 1. NNT derived from the meta-analyses of trials of prophylactic antiemetics in surgery for strabismus in children

Medication	NNT (95% CI)	NNT_{Lost}, LOI when $NNT_T = \infty$	NNT_{Lost}, LOI when $NNT_T = NNT$
Droperidol 10	15.8 (NNT-b = 4, NNT-h = 8)	69.2, 22.8%	26.3, 60%
Droperidol 20	6.2 (NNT-b = 2.5, NNT-h = 13.9)	190, 3.3%	20.6, 30.1%
Droperidol 50	9.5 (NNT-b = 3.5, NNT-h = 13)	172.6, 5.5%	27.2, 34.9%
Droperidol 75	3.5 (2.8, 4.8)	>1,000, 0%	63.5, 5.5%
Metoclopramide 0.10	7.2 (NNT-b = 3.3, NNT-h = 44)	590.5, 1.2%	29.9, 24.1%
Metoclopramide 0.15	4.0 (2.7, 7.6)	>1,000, 0%	41.5, 9.6%
Metoclopramide 0.25	2.5 (1.8, 4.3)	>1,000, 0%	29.3, 8.5%
Dixyrazine 0.25	2.5 (1.5, 7.6)	>1,000, 0%	18.3, 13.7%
Ondansetron 0.15	2.5 (1.6, 5.2)	>1,000, 0%	23.7, 10.6%
Atropine 10	25.0 (NNT-b = 3.7, NNT-h = 5)	33.8, 73.9%	21.3, 117.2%
Lorazepam 10	14.3 (NNT-b = 4, NNT-h = 9)	84.6, 16.9%	27.3, 52.4%

Abbreviations: CI, confidence interval; NNT, number needed to treat; NNT-b, number needed to treat to benefit; NNT-h, number needed to treat to harm; NNT_T, threshold NNT; LOI, Lost Opportunity Index.

Data from Tramèr et al. [24] and Altman [13].

treatment decision by contrasting the effort of treatment vs. its benefit. Another motivation behind our approach was the difficulty in the presentation and interpretation of the CI for the NNT when the CI covers both the negative and positive values.

The novelty of our proposed approach is that it expresses uncertainty in a measure of treatment efficacy based on its impact on decision making and not based on a generic statistical paradigm. Although it may be impractical for clinicians to use opportunity loss measures, it should be feasible for health policy makers to apply the LOI and the Lost NNT in decision making. As outlined in more detail in the (Appendix, see appendix on the journal's Web site at www.jclinepi.com), it is possible to estimate the total number of instances a treatment decision will be made in the target population over a given time period [26], and to calculate how many suboptimal decisions will be made owing to lack of certainty in treatment efficacy [9].

We are aware of several limitations to the theory and practical implementation of the Lost NNT and LOI. For one, the present approach hinges on the assumption that a decision is always made based on using a treatment threshold [27]. If such a threshold is not rigorously defined, then the Lost NNT and LOI do not reflect the true opportunity loss. Furthermore, calculation of the Lost NNT and LOI is more difficult than other calculations proposed around the NNT. The Lost NNT and LOI require quantification of treatment threshold (NNT_T). Yet the NNT_T is a function of aspects of treatment that may themselves be uncertain, including costs and rate of adverse events. This means a rigorous quantification of the NNT_T will yield a probability distribution for its value. However, if the distribution of ARR_T as well as ARR are assumed to be normal, calculations can be performed analytically. The equations for the calculation of the Lost NNT and LOI can optionally incorporate uncertainty in the treatment threshold (Appendix, see appendix on the journal's Web site at www.jclinepi.com). Finally, the opportunity loss approach is based on the Bayesian paradigm as it models a true ARR whose value can be guessed from the observed data. In the examples throughout this article, we have taken the sample distribution of the ARR as its probability distribution. This is an approximation that a rigorous analyst can obviate by directly estimating the posterior distribution of the ARR from the observed data. One may also incorporate informative priors at this stage, combining external evidence or expert opinion with the empirical results.

We conclude that quantifying opportunity loss around treatment decisions by using measures developed in this work can provide a measure of uncertainly that is directly relevant to the decision-making task, with particularly useful applications at the policy level. In many health jurisdictions, the demand for new treatments and the demand for evidence to support those new treatments ultimately compete with each other as they are funded from a fixed, limited health care budget. Measures such as the Lost NNT and LOI have the appeal of expressing the value of acquiring evidence in the same metric as the value of making a treatment decision. This enables decision makers to predict returns on investment in treatment efficacy studies in the same metric as the return on investment in adopting treatments [28]. We anticipate this work will stimulate further investigation and help bridge the gap between the principles of optimal decision making and the real practice of making decisions.

Acknowledgment

The authors would like to thank Ms. Stephanie Harvard and Ms. Jenny Leese for their editorial assistance.

Appendix

Supplementary material

Supplementary data associated with this article can be found, in the online version, at 10.1016/j.jclinepi.2012.01.022.

References

[1] Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. BMJ 1995;310:452−4.
[2] Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. N Engl J Med 1988;318:1728−33.
[3] Walter SD. Number needed to treat (NNT): estimation of a measure of clinical benefit. Stat Med 2001;20:3947−62.
[4] Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. BMJ 1999;319: 1492−5.
[5] Zermansky A. Number needed to harm should be measured for treatments. BMJ 1998;317:1014.
[6] Rembold CM. Number needed to screen: development of a statistic for disease screening. BMJ 1998;317:307−12.
[7] Kelly H, Attia J, Andrews R, Heller RF. The number needed to vaccinate (NNV) and population extensions of the NNV: comparison of influenza and pneumococcal vaccine programmes for people aged 65 years and over. Vaccine 2004;22:2192−8.
[8] Heller RF, Dobson AJ, Smeeth L, Ebrahim S. Disease impact number and population impact number: population perspectives to measures of risk and benefit/commentary: DINS, PINS, and things—(2);clinical and population perspectives on treatment effects. BMJ 2000;321: 950−3.
[9] Attia J, Page J, Heller RF, Dobson AJ. Impact numbers in health policy decisions. J Epidemiol Community Health 2002;56:600−5.
[10] Guyatt GH, Sackett DL, Sinclair JC, Hayward R, Cook DJ, Cook RJ. Users' guides to the medical literature. IX. A method for grading health care recommendations. Evidence-Based Medicine Working Group. JAMA 1995;274:1800−4.
[11] Sinclair JC, Cook RJ, Guyatt GH, Pauker SG, Cook DJ. When should an effective treatment be used? Derivation of the threshold number needed to treat and the minimum event rate for treatment. J Clin Epidemiol 2001;54:253−62.
[12] Travis CB, Phillippi RH, Tonn BE. Judgment heuristics and medical decisions. Patient Educ Couns 1989;13:211−20.

[13] Altman DG. Confidence intervals for the number needed to treat. BMJ 1998;317:1309−12.
[14] Newcombe RG. Confidence intervals for the number needed to treat. Absolute risk reduction is less likely to be misunderstood. BMJ 1999;318:1765−7.
[15] Claxton K. The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies. J Health Econ 1999;18:341−64.
[16] Felli J, Hazen G. Sensitivity analysis and the expected value of perfect information. Med Decis Making 1998;18:95−109.
[17] Stinnett AA, Paltiel AD. Estimating CE ratios under second-order uncertainty: the mean ratio versus the ratio of means. Med Decis Making 1997;17(4):483−9.
[18] Bender R. Calculating confidence intervals for the number needed to treat. Control Clin Trials 2001;22:102−10.
[19] Brown LD, Cai TT, DasGupta A. Interval estimation for a binomial proportion. Stat Sci 2001;16:101−17.
[20] Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. Stat Med 1998;17:873−90.
[21] Hashemi L, Nandram B, Goldberg R. Bayesian analysis for a single 2×2 table. Stat Med 1997;16:1311−28.
[22] Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4:213−26.
[23] Buckland ST. Monte Carlo confidence intervals. Biometrics 1984;40: 811−7.
[24] Tramèr M, Moore A, McQuay H. Prevention of vomiting after paediatric strabismus surgery: a systematic review using the numbers-needed-to-treat method. Br J Anaesth 1995;75:556−61.
[25] Claxton K, Lacey L, Walker S. Selecting treatments: a decision theoretic approach. J R Stat Soc A 2000;163:211−25.
[26] Philips Z, Claxton K, Palmer S. The half-life of truth: what are appropriate time horizons for research decisions? Med Decis Making 2008;28:287−99.
[27] Thornton JG, Lilford RJ, Johnson N. Decision analysis in medicine. BMJ 1992;304:1099−103.
[28] Fenwick E, Palmer S, Claxton K, Sculpher M, Abrams K, Sutton A. An iterative Bayesian approach to health technology assessment: application to a policy of preoperative optimization for patients undergoing major elective surgery. Med Decis Making 2006;26:480−96.