Eur J Med Res (2005) 10: 18-22

INCREMENTAL COST EFFECTIVENESS EVALUATION IN CLINICAL RESEARCH*

F. Krummenauer, I. Landwehr

Clinical Epidemiology and Health Economy Unit, University Hospital for Orthopedics, Technical University of Dresden (Head of the department: Prof. Dr. K.-P. Günther), Dresden, Germany

Abstract
Objective: The health economic evaluation of therapeutic and diagnostic strategies is of increasing importance in clinical research. Therefore also clincial trialists have to involve health economic aspects more frequently. However, wheras they are quite familiar with "classical" effect measures in clinical trials, the corresponding parameters in health economic evaluation of therapeutic and diagnostic procedures are still not this common.
Methods: The concepts of incremental cost effectiveness ratios (ICERs) and incremental net health benefit (INHB) will be illustrated and contrasted along the cost effectiveness evaluation of cataract surgery with monofocal and multifocal intraocular lenses. ICERs relate the costs of a treatment to its clinical benefit in terms of a ratio expression [indexed as € per clinical benefit unit]. Therefore ICERs can be directly compared to a pre-specified willingness to pay (WTP) benchmark, which represents the maximum costs, health insurers would invest to achieve one clinical benefit unit. INHBs estimate a treatment's net clinical benefit after accountig for its cost increase versus an established therapeutic standard. Ressource allocation rules can be formulated by means of both effect measures.
Results: Both the ICER and the INHB approach enable the definition of directional ressource allocation rules. The allocation decisions arising from these rules are identical, as long as the willingness to pay benchmark is fixed in advance. Therefore both strategies crucially call for a priori determination of both the underlying clinical benefit endpoint (such as gain in vision lines after cataract surgery or gain in quality-adjusted life years) and the corresponding willingness to pay benchmark.
Conclusion: The use of incremental cost effectiveness and net health benefit estimates provides a rationale for health economic allocation discussions and founding decisions. It implies the same requirements on trial protocols as yet established for clinical trials, that is the a priori definition of primary hypotheses (formulated as an allocation rule involving a pre-specified willingness to pay benchmark) and the primary clinical benefit endpoint (as a rationale for effectiveness evaluation).

Key words: cost effectiveness, incremental costs, cataract surgery, multifocal lenses

1. INTRODUCTION

Meanwhile therapeutic and diagnostic procedures are not only evaluated from a clinical, but also from a health economic point of view to link their clinical efficacy to the underlying direct costs. Therefore cost effectiveness analysis becomes increasingly important both for clinicians and for administratives of the health care system. Discussions on ressource allocation or on the founding of medical supplementation can be based on the results of such cost effectiveness evaluations and therefore provide an objective rationale for decisions.

Regarding the impact of such decisions it becomes obvious, that health economic evaluations must not be performed in a less confirmatory or less valid manner than yet established for the evaluation of clinical trials. From this point of view, methodological requirements for health economic evaluations emerge. However, whereas clinical investigators and methodologists meanwhile are quite familiar with measures of efficacy in clinical trials (such as the Number Needed to Treat of a new treatment), corresponding measures for health economic evaluation still seem to be less established. Therefore, this review seeks to point out two common approaches of cost effectiveness evaluation. These concepts will be contrasted along their advantages in interpretation, but also concerning possibly liberal results when being used as a rationale for allocation decisions without sensitive consideration of the confirmatory nature of cost effectiveness evaluation. An application to the health economic evaluation of multifocal lens supplementation of cataract patients will illustrate the interpretation of these measures. Note, however, that the following scenario is also a valid basis for the evaluation of, for example, preventive strategies in glaucoma research or diagnostic procedures in refractive surgery. In general, two therapeutic or diagnostic alternatives will be contrasted by means of their relative cost effectivenss.

*The paper was presented during the m 102nd meeting of the German Ophthalmological Society (DOG), Berlin, in September 2004

2. Material and Methods

The following section will briefly parameterize the evaluation setting for the health economic comparison of a new therapy with an established standard with respect to the alternatives' relative cost effectiveness.

2.1 Cost Effectiveness Parameterization

The following will consider two therapeutic alternatives 1 and 2, where treatment 1 denotes an established standard procedure and treatment 2 is under discussion concerning possible recommendation for founding by health care insurers. A reasonable scenario will only consider a treatment alternative, costs of which exceed the costs of the standard treatment, and efficacy of which was already proven to be better than the standard's efficacy. This efficacy shall be characterized by a suitable clinical benefit endpoint like the gain in visual acuity lines in cataract surgery or the incidence reduction of progression rates in glaucoma prevention. If then K_1 and K_2 denote the treatments' costs and E_1 and E_2 the treatments' respective efficacies, the following will assume $K_2 > K_1$ and $E_2 > E_1$ (such a treatment alternative 2 is usually called "admissable" for ressource allocation). A cost effectiveness comparison of these treatments may then provide a decision on when to found treatment 2 instead of treatment 1, or when to retain ressource allocation to the standard treatment 1.

Incremental cost effectiveness

The ratio K / E is refered to as the cost effectiveness ratio (CER) and describes a treatment's marginal costs per gained clinical benefit unit: If, for example, the costs for cataract surgery are estimated 1250 € and a gain in visual acuity of 5 lines is achieved, the marginal costs of cataract surgery result as CER = 1250 € / 5 lines = 250 € per gained line.

Furthermore the incremental cost effectiveness ratio (ICER) of a treatment 2 versus the standard treatment 1 is defined as $ICER = (K_2 – K_1) / (E_2 – E_1)$ and estimates the additional costs, which must be invested to achieve one additional clinical benefit unit under treatment 2 instead of the standard. If, for example, the costs for supplementation of a cataract patient with a monofocal intraocular lens are estimated 1250 € versus 1750 € for multifocal lens supplementation, but a gain of 10 quality adjusted life years (QALYs) after multifocal surgery versus 5 QALYs after monofocal surgery is achieved, the incremental costs of multifocal cataract surgery versus monofocal surgery result as ICER = (1750 € - 1250 €) / (10 QALYs – 5 QALYs) = 500 € / 5 QALYs = 100 € additional costs per additionally gained quality-adjusted life year. In this sense, the ICER concept allows for "health economical ranking" of different services in ophthalmology, when being contrasted to the same standard service.

Ressource allocation rules can now be formulated straigt-forward: If a health care insurer considers treatment 2 for founding, an allocation rule based on the ICER could use a pre-specified benchmark μ, which characterizes the insurer's maximum willingness to pay (WTP) additional treatment costs per gained benefit unit. Therefore treatment 2 would be founded as soon as $\mu > ICER$, whereas treatment 1 remains founded otherwise. It is obvious that this rule essentially depends on the underlying willingness to pay parameter μ.

Net health benefit

A second concept for cost effectiveness evaluation is based on net health benefit estimation: The net health benefit (NHB) of a treatment is defined as its clinical benefit after correction for its incremental costs when being contrasted to a standard, i.e.: $NHB = E – K/\mu$, where μ denotes the above willingness to pay benchmark. Therefore the net health benefit approach directly involves the WTP model parameter into cost effectiveness estimation: If, for example, the costs for cataract surgery are estimated 1250 €, a gain in visual acuity of 5 lines is achieved, and a health insurer would invest up to 300 € per gained vision line (μ=300 € / line), the net health benefit of cataract surgery results as NHB = 5 lines – 1250 € / 300 €/line = 5 lines – 4.16 lines = 0.84 lines. A NHB of 0.84 lines indicates a small, but still positive net benefit of cataract surgery from this health insurer's perspective, even after correction for his willingness to pay philosophy.

A new treatment alternative's incremental net health benefit versus a standard is then defined as $INHB = NHB_2 – NHB_1$ and measures the additional clinical benefit of treatment 2 after correction for the two treatment alternatives' relative cost effectiveness. A NHB-based allocation rule suggests founding of treatment 2 as soon as $INHB > 0$ (thereby $NHB_2 > NHB_1$ by definition) and founding of treatment 1 otherwise.

It is easy to show, that the ICER-based and the INHB-based allocation rules yield the same allocation decisions, as long as the willingness to pay parameter μ remains fixed.

2.2 Implementation for clinical data

The cost and benefit information can be estimated by their population means and standard significance tests can be applied to the above allocation rules. If futher a multiple significance level $\alpha > 0$ is given, the allocation rules can be implemented as follows:

1. Determine $\mu > 0$ in advance.
2. Estimate the sample cost and efficacy estimates K and E and compute the NHB-estimates in terms of K and E via $NHB = E – K/\mu$ for both therapies.
3. Estimate the incremental net health benefit $INHB = NHB_2 – NHB_1$ of treatment 2 versus the standard treatment 1.
4. Perform a one-sided significance test to ensure $INHB > 0$. Formally, a statistically significant superiority in cost effectiveness of the new treatment 2 over the standard treatment 1 is ensured, when this test's p-value $p \leq \alpha/2$.

Implementation of this allocation rule becomes feasible by application of any common statistics software. Since the INHB-based allocation rule provides the same statistical decision as does the ICER-based one, the above implemenatation also contains an ICER-

based allocation rule (which, however, cannot be implemented quite as easy).

2.3 Cataract Surgery Data

The above allocation rule(s) will be illustrated in terms of the cost effectiveness evaluation of the supplementation of cataract patients with multifocal intraocular lenses. One drawback of monofocal intraocular lenses consists in the frequent ongoing need for seeing aids after surgery, for example for reading or driving. Multifocal lenses often overcome the need for such additional seeings aids. An increase in subjective quality of life can be expected [Orme et al. 2003].

German health care insurers reimburse the costs of monofocal lens supplementation, where a cost effectiveness ratio of CER = 223 € per gained vision line after surgery (interquartile range 129 – 348 €) was estimated [Landwehr et al. 2003]. However, founding of multifocal cataract surgery is still under discussion. To assess the incremental cost effectiveness of multifocal lens supplementation with respect to its putative quality of life benefit, data of a randomized trial in cataract patients [Krummenauer et al. 2002] have been re-analysed from a health economic point of view. For the sake of effect illustration the following clinical data was simulated, but simulation was strictly according to the effects of the underlying trial findings. Quality of life in this trial was assessed by means of the "Mainz questionnaire for quality of life in ophthalmological patients" [Krummenauer et al. 2003], which provides a utility value ranging from 0.0 to 1.0 (maximum quality of life). 400 patients were assigned to either a monofocal or multifocal lens supplementation, and a 6 months follow up on complications and post surgical quality of life was performed. Patients were interviewed by means of the Mainz questionnaire 4 weeks before and 6 months after initial surgery. The treatment groups' median age was 62 versus 64 years, which implied an assumed median life expectany of 23 and 21 years for quality adjusted life years (QALYs) computation. Costs were computed alongside a model patient's direct treatment cost for surgery, anaesthesia etc [Orme et al. 2003] and corrected for individually founded costs due to necessary seeing aids during the follow up. The WTP benchmark was fixed at 800 € per gained QALY.

3. Results

Table 1 displays the simulated median costs and benefits as well as the ICER and INHB estimates for both multifocal and monofocal lens supplementation. It shows a remarkable difference in both costs and gained QALYs, whereas already the marginal cost effectiveness of supplementation with multifocal lenses (852 € per gained QALY) turns out worse than the corresponding monofocal estimate of 786 € per gained QALY. Note that the net health benefit of multifocal cataract surgery turned out negative as well, i.e. its marginal cost effectiveness is in fact characterized by financial losses when corrected for the insurer's willingness to pay benchmark μ = 800 € per QALY.

In summary, the net health benefit after adjustment for the rather high willingness to pay benchmark illustrates a rather limited net benefit for both procedures. If only applied to median point estimates, the ICER-based allocation rule would still decide founding of monofocal intraocular lenses, but no longer consider multifocal supplementation, since ICER = 1060 € / QALY > 800 € / QALY = μ. The INHB-based allocation rule would yield the same decision: INHB = NHB (multifocal) – NHB(monofocal) = -0.133 QALYs – 0.028 QALYs = -0.161 QALYs < 0, i.e. multifocal cataract surgery results in a (slight) loss in cost effectiveness when contrasted to the monofocal therapeutic standard.

If the strategy in Section 2.2 is applied at a 5% significance level, a p-value of 0.045 (one-sided two sample Wilcoxon test) results, which has to be compared to the formal significance border 0.025 = 5%/2. Since p = 0.045 > 0.025, no statistically significant difference in net health benefits was found between the multifocal and monofocal lens supplementation, where benefit was based on the number of QALYs achieved by the respective treatments. Therefore supplementation of cataract patients with multifocal intraocular lenses cannot be ensured to show a significantly positive net health benefit as compared to the monofocal supplementation standard.

However, this does not imply an indication for founding multifocal lens supplementation: The latter could only be achieved by a significant test result on a positive incremental net health benefit! Since the latter even turned out negative, the data at hand does not provide a health economic rationale for the recom-

Table 1. Simulated sample medians of direct costs [€], clinical benefit [QALY = quality adjusted life years], cost effectiveness ratios (CER), incremental cost effectiveness ratios (ICER), net health benefits (NHB) and incremental net health benefits (INHB) for the supplementation of cataract patients with monofocal and multifocal intraocular lenses, where monofocal lenses are the standard supplementation.

	monofocal (n = 197)	**multifocal (n = 185)**
costs [€]	1250	1738
QALYs gained	1.59	2.04
CER [€ / QALY]	786	852
ICER [€ / QALY]		1060
NHB [QALY]	0.028	-0.133
INHB [QALY]		-0.161

mendation of founding multifocal intraocular lens supplementation in cataract surgery.

4. Discussion

The correct and flexible use of cost effectiveness measures will soon be a standard requirement to clinical and epidemiological trials. Therefore this text seeked to review two established health economic measures, which yield the same financial ressource allocation decision, when cost effectiveness of treatment alternatives is intended as a rationale. Ranking of treatment alternatives becomes feasible and allocation decisions are more transparent.

Clinical considerations

Recent ophthalmological literature focused the cost effectiveness of cataract surgery, where a cost effectiveness ratio (CER) of 2020 U.S. $ per gained QALY for initial cataract surgery based on monofocal intraocular lenses was found [Busbee et al. 2002]. Independently, the incremental costs for multifocal lens supplementation were estimated about 30 U.S. $ per score point in a self-rating scale on patients' quality of vision satisfaction.

Note that the latter result does not contradict the above incremental cost estimate (1060 € per QALY), as completely different benefit endpoints were used in the respective investigations. Regarding the long-time benefit of cataract surgery, the computation of quality-adjusted life years, however, seemed somewhat more appropriate. Furthermore, a self-rating score such as used by Orme et al. to estimate the benefit in ophthalmological patients rather estimates a subjective patient satisfaction with the surgical procedure's outcome than its efficacy in terms of quality of life improvement. The different magnitudes of the resulting parallel findings illustrate the crucial need for a priori determination of the clinical benefit endpoint before starting the intended cost effectiveness evaluation. Both results have their own correct interpretation, but are hardly comparable among each other. Hoewever, for comparison with the cost effectiveness information on initial cataract surgery the incremental costs per QALY are appropriate: Initial cataract surgery based on monofocal lenses means an investion of 2020 $ per gained QALY, whereas the supplementation with multifocal lenses would afford the investion of additional 1113 $ (= 1060 €) per QALY.

Statistical considerations

Whereas the ICER-based approach provides somewhat attractive information (the indexing with € per gained benefit unit appears to be instructive to both clinical researchers and methodologists), its statistical feasibility has to be based on severe model assumptions. Recent methodological literature has devoted a lot of attention to the interval estimation of ICERs: Whereas the interval estimation of ICERs is yet elaborate under the assumption of normally distributed cost and efficacy data [Heitjan 2000; Siegel et al. 1996; Wakker et al. 1995], the problem of ratio estimation remains merely unsolved for the more realistic application to skewed cost data.

Maybe this methodological problem in ICER estimation is one of the reasons, why the NHB approach found increasing acceptance among methodologists during the past years. In this context it is overly important, that the allocation rules based on the net health benefit approach yield the same allocation decisions as the ICER-based ones, since interval estimation in the NHB context can be reduced to linear statistics and standard univariate significance testing and interval estimation. Therefore the rather difficult interpretation of (I)NHB estimates becomes weakened by their advantages concerning statistical feasibility. On the other hand, communication of NHB estimates should be handled with care: Note, that the NHB point estimates in the cataract surgery example do not even slightly mirror the order of the underlying willingness to pay parameter μ (although being computed by imputation of this parameter μ = 800 € per QALY)! This motivates the integration of methodologists into both the planning and evaluation phase of cost effectiveness investigations.

It appears to be a challenge for clinicians and methodologists to implement trials on cost effectiveness of the various offers in medicine to achieve a rationale for allocation discussion based on incremental cost effectiveness measures such as indicated above.

5. Conclusion

The confirmatory definition of clinical endpoints, clinically relevant effects and significance levels during the planning of clinical trials is yet common standard among clinical investigators. The corresponding a priori determination of clinical benefit endpoints, allocation significance levels and willingness to pay benchmarks needs to become a standard as well in both planning and reporting cost effectiveness investigations in ophthalmology.

Acknowledgement: The authors are grateful to Ms Karen Faulkner (medical student) for a native speaker revision of the first draft of this manuscript.

References

Busbee BG, Brown MM, Brown GC, Sharma S (2002) Incremental cost-effectiveness of initial cataract surgery. Ophthalmology 109:606-13

Heitjan DF (2000) Fieller's method and net health benefits. Health Econ 9:327-35

Krummenauer F, Dick HB, Tehrani M, Blümle S, Ott H (2002) Randomisierte Studie zum Vergleich der Auftrittshäufigkeiten nach Implantation monofokaler bzw. multifokaler Intraokularlinsen unter Adjustierung an den Einfluss der Vorinformation durch den aufklärenden Arzt. Ophthalmologe 99 (suppl 1):1116-7

Krummenauer F, Lohmeier A, Dick HB (2003) Quality of Life after cataract surgery – results of a prospective follow during 04/2001 – 06/2002. Ophthalmologe 100: 1054-61

Landwehr I, Tehrani M, Dick HB, Krummenauer F (2003) Cost effectiveness evaluation of cataract patient care in respect of monofocal intraocular lenses from the perspective of German statutory health insurances. Klin Monatsbl Augenheilkd 220:532-9

Laska EM, Meissner M, Siegel C, Wanderling J (2001) Statistical cost effectiveness analysis of two treatments based on net health benefits. Stat Med 20:1279-1302

Orme ME, Paine AC, Teale CW, Kennedy LM (2002) Cost effectiveness of the AMOArray multifocal intraocular lens in cataract surgery. J Refract Surg 18:162-8

Siegel C, Laska E, Meissner M (1996) Statistical methods for cost-effectiveness analysis. Controlled Clin Trials 17:387-406

Wakker P, Klaassen MP (1995) Confidence intervals for cost-effectiveness ratios. Health Econ 4:373-81

Received: September 13, 2004 / Accepted: November 24, 2004

Address for correspondence:
Prof. Dr. Frank Krummenauer
Abteilung für Klinische Epidemiologie und Gesundheitsökonomie an der Klinik und Poliklinik für Orthopädie
Universitätsklinikum Carl Gustav Carus an der Technischen Universität Dresden
Fetscherstr. 74, Haus 29
D-01309 Dresden, Germany
Tel.: +49(0)351/458 3747
E-mail.: Frank.Krummenauer@uniklinikum-dresden.de