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Economic Evaluations and Randomized Trials in Spinal Disorders: Principles and Methods

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Study Design. Descriptive methodologic recommendations.

Objective. To help researchers designing, conducting, and reporting economic evaluations in the field of back and neck pain.

Summary of Background Data. Economic evaluations of both existing and new therapeutic interventions are becoming increasingly important. There is a need to improve the methods of economic evaluations in the field of spinal disorders.

Materials and Methods. To improve the methods of economic evaluations in the field of spinal disorders, this article describes the various steps in an economic evaluation, using as example a study on the cost-effectiveness of manual therapy, physiotherapy, and usual care provided by the general practitioner for patients with neck pain.

Results. An economic evaluation is a study in which two or more interventions are systematically compared with regard to both costs and effects. There are four types of economic evaluations, based on analysis of: (1) cost-effectiveness, (2) cost-utility, (3) cost-minimization, and (4) cost-benefit. The cost-utility analysis is a special case of cost-effectiveness analysis. The first step in all these economic evaluations is to identify the perspective of the study. The choice of the perspective will have consequences for the identification of costs and effects. Secondly, the alternatives that will be compared should be identified. Thirdly, the relevant costs and effects should be identified. Economic evaluations are usually performed from a societal perspective and include consequently direct health care costs, direct nonhealth care costs, and indirect costs. Fourthly, effect data are collected by means of questionnaires or interviews, and relevant cost data with regard to effect measures and health care utilization, work absenteeism, travel expenses, use of over-the-counter medication, and help from family and friends, are collected by means of cost diaries, questionnaires, or (telephone) interviews. Fifthly, real costs are calculated, or the costs are estimated on the basis of real costs, guideline prices, or tariffs. Finally, in the statistical analysis the mean direct, indirect, and total costs of the alternatives are compared, using bootstrapping techniques. Incremental cost-effectiveness ratios are graphically presented on a cost-effectiveness plane and acceptability curves are calculated.

Conclusion. Economic evaluations require specific methods. These recommendations may be helpful in improving the quality of economic evaluations of new and existing therapeutic interventions in the field of spinal disorders. [Key words: economic evaluations, cost-effectiveness, methodology, musculoskeletal disorders] Spine 2004;29:442–448

As a result of the limited availability of financial resources, there is an increasing demand to improve the efficiency of health care, and an increasing number of economic evaluations are performed to meet this demand. Economic evaluation in health care can be defined as the comparative analysis of alternative interventions in terms of both their costs and consequences (risks). The main tasks involved in any economic evaluation are identifying, measuring, valuing, and comparing the costs and consequences of new or existing interventions. The central question in any type of economic evaluation is whether the extra effects of an intervention are worth the extra costs. An intervention with high costs can still be efficient, provided that the effects of the intervention are also substantial. In other words, the intervention with the lowest costs is not necessarily the most efficient.

A variety of preventive, diagnostic, and therapeutic interventions are commonly used for patients with spinal disorders, and numerous randomized trials and systematic reviews have evaluated the effectiveness of these interventions. Because spinal disorders have a major impact on society in terms of total health care expenditure, work absenteeism, and disablement, it is also important to obtain insight into the efficiency of these interventions. As yet, only a few reports on full economic evaluations in this field have been published and their methodologic quality is generally poor. This article discusses the theory and the methodology underlying economic evaluations in an attempt to improve the quality of future economic evaluations in the field of spinal disorders. An example is used to illustrate an economic evaluation that we recently performed alongside a pragmatic randomized controlled trial in which patients with neck pain were treated with manual therapy, physiotherapy, or continued care provided by the general practitioner (GP).
nomic evaluations are partial evaluations, in which only the costs or costs and effects of one intervention are described, or in which the costs of two or more interventions are compared. Only with full economic evaluations, in which the costs and effects of two or more interventions are compared, can questions about efficiency be answered. This article focuses on full economic evaluations performed concurrent with randomized controlled trials. Examples of partial evaluations are two observational studies in which the costs of back and neck pain have been estimated.

In Table 1, the four most commonly used methods for full economic evaluations are listed. The designs of these studies are similar, and the main difference is the outcome measures that are used to determine efficiency.

**Cost-Effectiveness Analysis**
Cost-effectiveness analysis involves the difference in costs of two or more interventions related to the difference in effects. The effects are usually primary clinical outcomes, i.e., intensity of pain, disability, and general improvement.

**Cost-Utility Analysis**
Cost-utility analysis is a special case of cost-effectiveness analysis. The difference in costs of two or more interventions is related to the difference in utilities. A utility refers to the preference that individuals or society may have for any particular set of health outcomes. A cost-utility analysis is particularly useful because it allows for quality-of-life adjustments to a given set of intervention outcome measures, and it provides a generic outcome measure for comparison of costs and outcomes between different interventions and diseases. The results of cost-utility analyses are typically expressed in terms of costs per quality-adjusted life-year (QALY) or disability-adjusted life-year (DALY).

**Cost-Minimization Analysis**
This economic evaluation is a special form of cost-effectiveness analysis, in which the effects of the interventions being compared are equal. Consequently, only the difference in costs is evaluated.

**Cost-Benefit Analysis**
The difference in costs of two or more interventions is related to the difference in financial benefits. Sometimes it cannot be assured that the consequences of alternative interventions and for different diseases are identical. In addition, it is sometimes not possible to reduce the outcomes of interest to a single effect that is common to both interventions. The consequences of an intervention may then be expressed in terms of their financial benefits to facilitate comparison between the interventions; for example, using the willingness-to-pay principle.

It may not always be possible to predict in advance which type of economic evaluation will be performed, because this may depend on the results of an associated clinical evaluation. Furthermore, various approaches are sometimes used simultaneously, because each individual approach explores a different dimension. However, cost-effectiveness and cost-utility analyses are the most commonly used types of economic evaluation in the field of spinal disorders.

**Study Design**
The design of an economic evaluation consists of several steps:

1. Identification of the perspective
2. Identification of the alternatives
3. Identification, measurement, and valuation of effects
4. Identification, measurement, and valuation of costs
5. Statistical analysis

**Identification of the Perspective.** An economic evaluation can be performed from different perspectives, and the perspective chosen determines the design of the evaluation. An economic evaluation is usually performed from a societal perspective, in which all relevant costs and effects are measured, regardless of who pays the costs and who benefits from the effects. However, an economic evaluation can also be performed from a narrower perspective, such as the perspective of insurance companies, hospitals, physicians, or patients. From the perspective of patients, for example, only the out-of-pocket expenses for over-the-counter medication or visits to alternative and complementary therapists are important.

In the economic evaluation comparing manual therapy, physiotherapy and continued care provided by the
GP for patients with neck pain, a societal perspective was chosen. All direct and indirect costs were included in the economic evaluation.6

Identification of the Alternatives. In an economic evaluation, two or more preventive, diagnostic, or therapeutic interventions are compared. The experimental intervention should be compared with another intervention, preferably to usual care or the best available alternative.1,2 The comparison intervention, however, can also be the cheapest alternative, a rival product, a placebo, or no treatment. Ideally, a new intervention should only be implemented if it is proven to be more efficient than the best available alternative. Coexisting interventions can also be compared in an economic evaluation to determine the most efficient intervention for the patients. There are strict regulations regarding the introduction of new medication, including the choice of the comparative intervention in pharmacoeconomic evaluations.9–11 As yet there are no such regulations for other new products or nonpharmaceutical interventions (e.g., new exercise regimes or new surgical techniques).

In the neck pain economic evaluation, three interventions (manual therapy, physiotherapy, and continued care provided by the GP) were compared. These interventions are the most commonly applied conservative methods of treatment for patients with neck pain in The Netherlands. At the start of the trial, it was unclear which intervention was the best available treatment option for patients with neck pain.6

Identification, Measurement, and Valuation of Effects. Before performing an economic evaluation, the relevant effects must be identified. In many cases, the economic evaluation will be conducted alongside a clinical study; for instance, a randomized clinical trial. The primary outcome measures of the clinical trial are also used in the economic evaluation. The outcome measures in trials on spinal disorders usually include the following domains: pain, disease-specific function, generic health status, work disability, and patient satisfaction.12

In addition to disease-specific outcome measures, most economic evaluations also include generic outcome measures. These generic outcome measures are usually less responsive but make it possible to compare the outcomes of a range of interventions for different diseases. Examples of health profiles are the SF-36,13 the Nottingham Health Profile (NHP),14 and the Sickness Impact Profile (SIP).15 Examples of commonly used health indexes are the EuroQol16 and the Health Utility Index (HUI).17 A health index can be used to calculate utilities, in which the effects are expressed as QALYs.18 Sometimes, DALYs are used. A DALY combines time lived with a disability and the time lost because of premature mortality.19

The economic evaluation of treatments for neck pain was conducted alongside a randomized clinical trial in which various outcomes were measured. Perceived recovery was measured on a 6-point scale, ranging from “completely recovered” to “much worse.” The severity of the main symptom and pain intensity were measured on an 11-point numerical rating scale, ranging from 0 to 10. The EuroQol was used to calculate utilities. Patients completed self-report questionnaires at baseline and after 3, 7, 13, 26, and 52 weeks.6

Identification, Measurement, and Valuation of Costs. The costs that are relevant for economic evaluations can be subdivided into direct health care costs, direct nonhealth care costs, and indirect costs.1 Direct health care costs are the costs of activities within the formal health care system that are directly related to the disease or disorder at issue; for instance, costs of physiotherapy, manual therapy, general practice care, medication, orthopedic care, and hospital admission. Direct nonhealth care costs are the costs of activities outside the formal health care system that are directly related to the disease or disorder. Examples are travel expenses to and from the hospital, the costs of over-the-counter medication, the costs of informal health care (care provided by the family), and the costs of devices. Indirect costs are costs that have no direct connection with the medical interventions, but are a consequence of it. Indirect costs within the health care system are the costs patients incur during the life-years gained. Indirect costs outside the health care system are the costs of production losses caused by work absenteeism, work disability, or death of a patient. Indirect costs can be calculated for patients with or without a paid job.

To measure the direct and indirect costs, information about the utilization of health care must be collected, for which various methods exist, such as questionnaires, diaries, interviews, patient files, and insurance company records. Typically, several methods are used simultaneously. The use of routine databases (i.e., in a hospital) may not always provide the necessary information, and the validity and reliability of the databases may not be very high. Ideally, the relevant data are collected prospectively; for example, by means of cost diaries, in which patients record every visit to a physician or therapist, the medication they use, and any work-absenteeism or inability to perform daily activities resulting from the disease at issue.20

To value medical consumption a number of prices can be used. The best way is to calculate real costs for at least the most important cost components. With this method the costs of personnel, materials, office space, depreciation, and overheads are charged to each intervention separately. In practice, however, it is not always possible to calculate real costs because of the limited availability of data. For example, to calculate the real costs of physiotherapy for low back pain, one would need to accurately calculate for each treatment session the costs of the physiotherapist, the costs of the materials used (for example the costs of towels, exercise equipment, etc.), and the costs of the office space and exercise room. Obviously, these costs are often difficult to calculate. Sometimes real costs are not calculated for practical reasons, i.e., the
enormous amount of time involved. There are some alternatives for the use of real costs, one of which is the use of tariffs. Tariffs are the result of negotiations between professional health care organizations and the government, and do not necessarily represent the real costs. Sometimes a shadow price can be used to estimate costs; for instance, for care provided by family or friends or if available guideline prices (based on real costs calculation) can be used.

The indirect costs of spinal disorders are usually substantial. Therefore, it is important that they are correctly estimated. There are two methods that can be used to evaluate production losses: the human capital approach (HCA) and the friction cost method (FCM). The HCA is the most frequently used method, in which the indirect costs are based on the total expected production losses for an individual worker. The productivity losses occur from the moment of absence until full recovery, and if no recovery, until the moment of death or retirement. The HCM does not take the replacement of the sick employee (at a certain maximum of work absenteeism) into account. The FCM is based on the principle that the total production losses depend on the time an organization needs to replace a sick employee, the so-called friction period.

Both methods do not take into account the reduced productivity of employees at their work. This is especially relevant for chronic spinal disorders in which periods of reduced productivity alternate with illness-related absence. Kessler and colleagues recently developed a self-report instrument to estimate the workplace costs of health problems in terms of reduced job performance, sickness absence, and work-related accidents. This instrument not only focuses on work absenteeism but also focuses on the reduced job performance of patients with a paid job and patients without a paid job. The number of days of work absenteeism or inability to perform daily activities must be valued for which the wages of the patients can be used. To make the indirect costs transparent for other situations/countries, it is important to report the number of work absenteeism days separately from the indirect costs.

The neck pain economic evaluation was performed from a societal perspective. Direct and indirect costs were measured by means of cost diaries for a total follow-up of 52 weeks. Direct costs included costs of visits to the physiotherapist, manual therapist, and GP, and hospitalization, surgery, and medication. Indirect costs were costs of work absenteeism for patients with a paid job and the inability to perform normal daily activities for all patients. As an example, Table 2 presents an overview of different cost components and real costs used in the economic evaluation for patients with neck pain. The indirect costs in this economic evaluation were calculated according to the FCM, in which work absenteeism per patient is restricted to a maximum number of days (122 days).6

### Statistical Analysis of Costs

Economic evaluations require specific statistical techniques. In a full economic evaluation, the costs and effects of two or more interventions are compared. The first step is to analyze the costs and the effects separately. Subsequently, the interventions are compared to determine whether the differences in costs and effects with a 95% confidence interval (CI) are statistically significant. The analysis of cost data are complicated by the typical skewness or nonnormality of the data, which is usually caused by high costs incurred by a few patients. The nonnormality of the distribution of cost data should be taken into account in the analysis. Despite the usual skewness in the distribution of costs, it is the arithmetic mean that is the most informative measure for health care policymakers. Measures other than the arithmetic mean provide no information about the total cost of treating all patients. In the literature, various methods that can be used to deal with the nonnormality of the cost data have been described, such as Student’s t test, a t test on log-transformed data, and truncation and nonparametric rank test (such as Mann-Whitney/Wilcoxon).

The preferred method for the analysis of cost data are bootstrapping, which does not make any assumptions regarding the normality of the data, the equality of the variances or the shape of the distributions. Bootstrapping is a data-based simulation method and uses the observed distribution of the cost data. It is therefore appropriate for any distribution of data but is especially useful when distributions are skewed and traditional statistical methods may fail. Patients are randomly chosen from a study population. The number of randomly chosen patients is usually the same as the patients in the study population. The sampling is performed with replacement, indicating that a patient can be chosen more than

#### Table 2. Prices Used in the Economic Evaluation of Treatments for Patients With Neck Pain

<table>
<thead>
<tr>
<th>Service</th>
<th>Price (Euro)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct health care costs</td>
<td></td>
</tr>
<tr>
<td>General practitioner</td>
<td>16.60</td>
</tr>
<tr>
<td>Manual therapist</td>
<td>25.90</td>
</tr>
<tr>
<td>Physiotherapy</td>
<td>18.15</td>
</tr>
<tr>
<td>Outpatient appointment</td>
<td>40.85</td>
</tr>
<tr>
<td>Hospitalisation (per day)</td>
<td>235.95</td>
</tr>
<tr>
<td>Cesar exercise therapist</td>
<td>17.70</td>
</tr>
<tr>
<td>Professional home care (per hr)</td>
<td>22.70</td>
</tr>
<tr>
<td>Direct nonhealth care costs</td>
<td></td>
</tr>
<tr>
<td>Alternative therapist (per visit)</td>
<td>27.20</td>
</tr>
<tr>
<td>Home care (per hr)</td>
<td>7.94</td>
</tr>
<tr>
<td>Help from partner/friends</td>
<td>7.94</td>
</tr>
<tr>
<td>Travel expenses (per km)</td>
<td>0.11</td>
</tr>
<tr>
<td>Indirect costs</td>
<td></td>
</tr>
<tr>
<td>Absenteeism paid labor (per day)</td>
<td>—</td>
</tr>
<tr>
<td>Absenteeism unpaid labor (per hr)</td>
<td>7.94</td>
</tr>
</tbody>
</table>

* Euro 1 = US $0.90.
** Tariff.
*** Price according to professional association.
† Indirect costs for paid labor were calculated on the basis of a mean income of the Dutch population according to age and sex.
once from the study population. For each resample, the
statistics of interest are calculated. The number of sam-
ples will depend on the measure of interest. The distri-
bution of these values of the statistic provides an approx-
imation to its population sampling and can be used to
calculate CIs.28,29 There are various methods that can be
used to calculate bootstrapped CIs for differences in
costs. Currently, the preference is for CIs obtained by
bias-corrected and accelerated (BCA) bootstrapping.28

In the neck pain economic evaluation, differences in
costs were calculated and CIs were obtained by BCA
bootstrapping. The mean total costs per patient for man-
ual therapy (Euro 447) were one third of the mean total
costs for physiotherapy (Euro 1,297) and continued care
provided by the GP (Euro 1,379). These differences were
statistically significant for manual therapy compared
with physiotherapy (mean difference: Euro, \(-850\); 95% CI:
2,258; \(-239\)) and for manual therapy compared to
continued care provided by the GP (mean difference:
Euro, \(-932\); 95% CI: 1,932; \(-283\)).6

**Incremental Cost-Effectiveness Ratio.** In an economic eval-
uation, the costs and effects of two interventions can be
directly evaluated by a cost-effectiveness ratio that indi-
cates what additional investments are necessary to gain
additional effects. Figure 1 presents a graph of the poten-
tial outcomes of the cost-effectiveness ratios.30 Note that
this figure can also be used for cost-utility ratios in which
effects are expressed as utilities.

If an intervention is more effective and less costly than
the alternative intervention to which it is compared, the
more effective and less costly intervention is dominant
and will obviously be preferred (Q-SE). If the alternative
intervention is less effective and more costly, the old in-
tervention will be preferred (Q-NW). If an intervention is
more effective and more costly (Q-NE) or less effective
and less costly (Q-SW), it is not immediately clear which
intervention should be preferred, and an incremental
cost-effectiveness ratio, cost-effectiveness plane, accept-
ability curve, or net health benefit should be calculated.

The CIs for the incremental cost-effectiveness ratio
can be calculated using the bias-corrected percentile
method.31,32 The interpretation of a cost-effectiveness
ratio with a 95% CI is difficult, and numerous problems
associated with an incremental cost-effectiveness ratio
and its 95% CI have been described.33,34 New methods
that try to avoid these problems have been developed; for
example, to present the results as a net health benefit or
an acceptability curve, which shows the probability that
a treatment is cost-effective at a specific ceiling ratio.35

In the neck pain economic evaluation, incremental
cost-effectiveness ratios were calculated. Manual therapy
was more effective and less costly than physiotherapy
and continued care provided by the GP. For example, the
incremental cost-effectiveness ratio for manual therapy
compared to physiotherapy for pain intensity was \(-757\).
Indicating that manual therapy has a better effect on pain
intensity with saving in costs (\(-757\)) compared to phys-
iotherapy. Figure 2 shows that 98% of the incremental
cost/effect pairs on the cost-effectiveness plane for this
ratio were located in the southeast quadrant (lower costs
and better effects). Therefore, it was concluded that man-
ual therapy was clearly dominant over physiotherapy.6

**Sample Size Calculations**

As stated previously, economic evaluations are often per-
formed alongside a randomized clinical trial. Sample
sizes in these trials are typically calculated to detect clini-
cally relevant differences in primary effect measures. To
calculate the sample size for an economic evaluation,
assumptions have to be made about the maximum
threshold value that will be accepted to obtain additional
effects or acceptable costs per outcome.36 It can be as-
sumed that the sample size required in an economic eval-
uation is very large, because of the large variation in cost
data compared with clinical effect measurements.34
Therefore, if sample size calculations are performed for
economic evaluations, then the clinical trial may become
too expensive, because of the large increase in the num-
ber of patients needed, or it might be unethical to include

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Figure 1. Cost-effectiveness
plane.30 Q-NW, Northwest quad-
rant; Q-NE, Northeast quadrant;
Q-SE, Southeast quadrant; Q-SW,
Southwest quadrant.
more patients than are needed to prove clinical effectiveness. Consequently, clinical trials will typically be underpowered for economic evaluations, even if the main clinical comparison is appropriately powered.

In the neck pain economic evaluation, the number of patients needed was based on a clinically relevant difference. No separate sample size calculation was performed for the economic evaluation. In this trial, manual therapy proved to be cost-effective, and the sample size of the clinical trial turned out to be large enough for the economic evaluation.

Sensitivity Analysis. The large number of assumptions that are made in most economic evaluations may strongly influence the results. It is customary to perform a sensitivity analysis in which the most important assumptions are varied to evaluate their impact on the conclusions. The ranges, and arguments for selecting these ranges, must be described. Briggs and Sculpher distinguish four types of uncertainty relating to: data sources of the study, extrapolation, the generalizability of the study results, and application of the appropriate analytical methods.

A one-way sensitivity analysis can be performed, in which the effect of varying a single variable on the conclusions is explored. A multiway sensitivity analysis, sometimes called a scenario analysis, varies more variables at the same time. The results of the sensitivity analysis will demonstrate the robustness of the findings and will help to improve the generalizability of the economic evaluation.

In the neck pain economic evaluation, a sensitivity analysis was performed by not using data on the patients who received surgery or were admitted to hospital. The sensitivity analysis showed the same results as the main analysis: manual therapy was more cost-effective than physiotherapy and continued care provided by the GP.

Modeling
Randomized trials in the field of spinal disorders usually have a follow-up of less than 1 year, although a few recent trials have included follow-up duration up to 3 or 5 years. If one is interested in estimating the economic impact of an intervention over a longer period than the time horizon of the trial, decision-analytic or microsimulation models can be used. The methods for using Markov models in health services research are well-documented. In a Markov model, a possible prognosis of a patient is split into a number of states. The probabilities of transition between states, costs, and effects can be varied over a specific timeframe. In a study, for example, evaluating the cost-effectiveness of nonsteroidal antiinflammatory drug (NSAID) side effects are important. In a randomized trial, the sample size may be too small to display adverse effects. However, adverse effects may be well-documented in the literature. A model simulation gives the opportunity to incorporate costs of adverse effects in an economic evaluation.

Conclusion
Economic evaluations are becoming increasingly important in health care research. In many cases, economic evaluations will be performed alongside clinical trials. It is important that an economic evaluation is fully integrated in the clinical trial and equally carefully designed. The study protocol must include considerations with regard to the perspective of the economic evaluation, identification, measurement and valuation of costs and effects, sample size, the power to detect relevant differences in economic variables, and an adequate length of follow-up.

Spinal disorders are not only a tremendous medical problem but also a socioeconomic burden. Economic evaluations help to identify the most efficient preventive, diagnostic, and therapeutic interventions for patients with spinal disorders and should play an important role in evidence-based medicine and health policy. Two reviews of published reports of economic evaluations in the field of low back pain concluded that the methodologic quality of the economic evaluations was poor.
Because policy-makers in their decision-making process use economic evaluations, it is of utmost importance that the information they provide is valid and reliable. Economic evaluations must be based on a specific study design and require specific statistical techniques. The aim of this article was to provide insight into the specific methodologic aspects of an economic evaluation and to present some practical guidelines for economic evaluations in the field of spinal disorders in line with the current state of the art. Hopefully, these recommendations will be helpful for researchers in conducting and publishing economic evaluations and for readers in critically appraising them.

**Key Points**

- Economic evaluations of existing and new therapeutic interventions are becoming increasingly important.
- There is a need to improve the methods of economic evaluations in the field of back and neck pain.
- Recommendations are provided for measuring, valuing, and analyzing cost data. These recommendations may be helpful in designing and conducting economic evaluations in the field of back and neck pain.

**References**