REVIEW ARTICLE

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Economic Evaluations of Cholesterol-Lowering Drugs

A Critical and Systematic Review

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Abstract

The wide availability of economic evaluations and their increasing importance for decision making emphasises the need for economic evaluations that are methodologically sound. The aim of this review was to provide users of economic evaluations of cholesterol-lowering drugs with an insight into the quality of these evaluations. By focusing on the most relevant studies, the gap between research and policy making may be narrowed.

A systematic review was conducted. All Dutch and English publications on economic evaluations of cholesterol-lowering drugs were identified by searching PubMed, the Centre for Reviews and Dissemination database (CRD), the NHS Economic Evaluation Database (NHS EED), the Health Technology Assessment database (HTA) and the Database of Abstracts of Reviews of Effects (DARE). A search strategy was set up to identify the articles to be included. The quality of these articles was assessed using Drummond's checklists. The scoring was performed by at least two reviewers. When necessary, disagreement between these reviewers was decided upon in a consensus meeting. We calculated an average quality score for the included articles.

The search identified 1390 articles, of which 23 were included. Most studies measured the costs per life-year gained. The overall score per study was disappointing and varied between 2.7 and 7.7, with an average of 5.5. Most studies scored high on the measurement of costs and consequences, whereas the establishment of effectiveness left room for improvement. Only two studies included a well performed incremental analysis.

This study noted an increase of quality of economic evaluations over time, suggesting the value of cost-effectiveness studies for policy decisions increases over time. In general, piggy-back evaluations tended to score higher on quality and may therefore be more valuable in decision making.

The WHO[1] predicts a large and global increase of cardiovascular disease (CVD), including coronary heart disease (CHD). Expectations for the next 2 decades are a 3-fold increase of ischaemic heart disease in Latin America, the Middle East and sub-Saharan Africa.[1,2] These expectations imply an increase in the financial pressures on healthcare services regarding both treatment and prevention of CVD. This increased financial burden of CVD prevention raises the question of cost effectiveness of drug therapy. Currently, an elevated risk of myocardial infarction (MI) and stroke is considerably lowered with (a combination of) drugs: lipid-lowering drugs (mainly HMG-CoA reductase inhibitors [statins]) for serum cholesterol lowering, blood pressure-lowering drugs and aspirin (acetylsalicylic acid).[1]

Hypercholesterolaemia is one of the major CVD risk factors, which is currently mainly treated with rather costly statins. Policy makers faced with priority setting and resource allocation in this area have to take both the health effects and the costs into consideration in the decision-making process. Numerous economic evaluations of lipid-lowering drugs have been performed over time in different countries. These analyses pertain to a broad spectrum of initial risk profiles and settings. The large availability of economic evaluations combined with the increased interest in economic evaluations underpins the need for evaluations that are methodologically sound.[3-5] The leading scoring system to assess the quality of economic evaluations is Drummond's checklist.[5] To our best knowledge there is one similar study by Gazzaniga and Garattini.[6] However, this study was published in 1992 and is outdated.

The aim of the present study was to systematically review the quality of economic evaluations of lipid-lowering drugs.

1. Method of Review

1.1 Search

The following databases were searched for relevant publications in Dutch and English: PubMed and the Centre for Reviews and Dissemination database (CRD); the latter is a compilation of the NHS Economic Evaluation Database (NHS EED), the Health Technology Assessment database (HTA) and the Database of Abstracts of Reviews of Effects (DARE), which contains part of the Cochrane Database.

Even though the NHS EED was searched, samples from other NHS databases, namely the main NHS database and the National Institute for Health and Clinical Excellence (NICE) database, were also used to assure full coverage.

Search terms included 'hypercholesterol(a)emia', 'hyperlipidaemia', 'cholesterol', 'statins', 'fibrates', 'bile acid sequestrants', 'lipids', 'cholesterol lowering' and 'lipid lowering', combined with 'economic evaluation', 'cost-effectiveness', 'cost-utility' or 'QALY'.

This search included all publications until October 2005.

1.2 Inclusion Criteria

To assure a minimum quality, studies were included if they (i) were a full economic evaluation (cost-effectiveness analysis and/or cost-utility analysis) of drug treatment of hypercholesterolaemia, (ii) used effectiveness data based on long-term outcome measurements from randomised, controlled trials (RCTs) [MI, stroke, etc.] and (iii) defined cost effectiveness and cost utility as costs per life-year gained (LYG) or costs per QALY gained.

A full economic evaluation is defined as an evaluation that compares two or more alternatives considering both the costs (including savings) and effects of an intervention.[5]

Studies were excluded if they (i) evaluated cotherapy for CVD risk factors even when this included treatment with lipid-lowering drugs, (ii) were restricted to those with familial hypercholesterolaemia, (iii) were not written in English or Dutch, or (iv) used surrogate endpoints to compare statin treatment with low-dose aspirin,[7] antihypertensive drugs or diets.

1.3 Analysis

Quality assessment is a subjective method; therefore, two reviewers assessed all publications included. The quality of different publications reporting the same study was assessed separately. The criteria/questions applied to the scoring system (see Appendix for details) were established in preliminary meetings of the two reviewers. All studies were reviewed independently. Disagreement between reviewers was decided upon in a consensus meeting.

As the discussion during the preliminary meetings showed, it was not always possible to provide clear answers to the questions in the checklist. Therefore, we scored the questions as follows: potential responses to the questions were adequate (score 1), partly adequate (score 0.5) or inadequate (score 0) [see Appendix]. Furthermore, these meetings showed that certain questions were redundant owing to the methodology used in the study. These were scored as 1.00. When it was impossible to rate a criterion/question based on the article it was assumed not to be favourable and scored as 0.00. Drummond's checklist provides an average score with each of the ten questions weighted equally. During the preliminary meetings, the criteria were decided all to be equally important to the overall quality of an article. Subsequently, the sub-criteria were regarded as equally important within a question. Therefore, the lowest overall score possible was 0.0 and the highest overall score possible was 10.0. The results were analysed by means of linear regression to determine whether there was a time trend in the quality scores of the included studies.

The results were ordered according to the 'best level of evidence principle' regarding the methods used to establish cost effectiveness. The best evidence of cost effectiveness would be a piggy-back evaluation. The second best option would be to base the cost-effectiveness assessment on effectiveness data derived from literature. Within this option, literature based on RCTs or meta-analysis of RCTs are preferred to literature based on observational studies. Our analysis did not include cost-effectiveness assessments based on observational studies.

2. Results of Review

2.1 Identification of Publications

Initially, our literature search identified 1390 publications. By reviewing titles and abstracts, 81 articles were selected. After reviewing the full papers, 23 articles were chosen.[8-30]

This review excluded 58 articles.[31-88] These did not comply with at least one of the inclusion criteria:

- did not measure the costs/LYG or costs/QALY gained: 26 studies,
- did not use effectiveness data based on long-term outcome measurements derived from RCTs: 49 studies,
- did not meet the inclusion criteria for the comparator: four studies,
- evaluated treatment other than the monotherapeutic drug treatment of hypercholesterolaemia: two studies, and
- derived the efficacy data from trials in patients with familial hypercholesterolaemia: one study.

Table I. Details of included economic evaluations of lipid-lowering drugs

Study	Comparator	Original data for effectiveness	Stated perspective	Country	Time horizon (y)	Discount rates (%)	Included costs	Base case ICER range[a]	Quality score
Primary prevention									
Piggy-back evaluation									
Caro et al.[14]	PL	WOSCOPS	NHS	UK	5	C = 6; E = 6	DM	£20 375/LYG	5.3
Caro et al.[23]	PL	WOSCOPS	NHS	Belgium UK	5	C = 5	DM	€29 900/LYG €31 400/LYG	7.2
Published data from RCTs									
Lim et al.[25]	NC	WOSCOPS	Health system	Australia	20	C = 3; E = 3	DM	$A(80 000–150 000)/LYG	5.7
Johannesson[28]	NC	WOSCOPS	Societal	Sweden	5	C = 5; E = 5	IDM and DM	$US(40 000–100 000 000)/QALY	5.1
Secondary prevention									
Piggy-back evaluation									
Scuffham and Chaplin[10]	NT	LIPS	NHS	UK	10	C = 6; E = 1,5	DM	€4352/LYG €4527/QALY	6.6
Glasziou et al.[8]	PL	LIPID	Health system	Australia	6	C = 5; E = 5	DM	$A10 938/LYG	6.4
Tsevat et al.[13]	PL	CARE	Societal	US	6	C = 3; E = 3	DM	$US(16 000–32 000)/LYG	6.8
Jonsson et al.[22]	PL	4S	NM	Sweden	5.4	C = 3; E = 3	DM	ECU5422/LYG	5.3
				Denmark				ECU5673/LYG	
				Norway				ECU3556/LYG	
				Finland				ECU8566/LYG	
				UK				ECU6476/LYG	
				Germany				ECU6928/LYG	
				France				ECU4243/LYG	
				Italy				ECU6002/LYG	
				Portugal				ECU6047/LYG	
				Belgium				ECU6743/LYG	
				Spain				ECU5504/LYG	
Muls et al.[18]	PL	PLAC	NM	Belgium US	3	C = 5; E = 5	DM	$US(13 274–24 359)/LYG $US(7124–12 665)/LYG	3.7
Johannesson et al.[16]	PL	4S	NM	Sweden	5	C = 5; E = 5	IDM and DM	$US(3800–27 400)/LYG	5.5
Ashraf et al.[27]	NC	PLAC	Societal	US	3	C = 5; E = 5	DM	$US(7124–12 665)LYG	3.8
Jonsson et al.[9]	PL	4S	Societal	Sweden	5.4	C = 5; E = 5	DM	£5502/LYG	5.6
				Norway				£6361/LYG	
				Belgium				£5165/LYG	
				France				£4137/LYG	
				Germany				£7827/LYG	

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Table I. Contd

Study	Comparator	Original data for effectiveness	Stated perspective	Country	Time horizon (y)	Discount rates (%)	Included costs	Base case ICER range[a]	Quality score
				Italy				£5869/LYG	
				Portugal				£8312/LYG	
				Spain				£6418/LYG	
				UK				£6983/LYG	
				Australia				£5970/LYG	
				NZ				£8824/LYG	
Published data from RCTs									
Chau et al.[21]	NC	CARE	Health system	China	5	C = 4 & 6; E = 6	DM	$HK65 280/LYG	5.2
Ganz et al.[30]	Usual care	CARE	Societal	US	Lifetime	C = 3; E = 3	DM	$US18 800/LYG	4.9
Riviere et al.[15]	Usual care	4S	Ministry of Health	Canada	15	C = 5; E = 5	DM	$US6108/LYG	5.7
Primary and secondary prevention									
Published data from RCTs									
Caro et al.[29]	NT	WOSCOPS	Policymakers	US	5	C = 3	DM	$US(1100–2900)/LYG	6.3
van Hout and Simoons[12]	PL	Meta-analysis	NM	The Netherlands	5	C = 5; E = 5	DM	€18 151/LYG	5.3
Prosser et al.[17]	NT	Review	Societal	US	30	C = 3; E = 3	DM	$US(1900–1 400 000)LYG	5.3
Pickin et al.[20]	NC	WOSCOPS/4S	NM	UK	Lifetime	C = 6; E = 6	DM	£(5100–12 500)/LYG	5.6
Hinzpeter and Lauterbach[24]	NC	CARE/4S	Societal	Germany	5	C = 4	DM	$US(40 800–74 700)/LYG	4.5
Pharoah and Hollingworth[19]	NC	WOSCOPS/4S	3rd party payer	UK	Lifetime	C = 5	DM	£(6000–361 000)/LYG	2.7
Type of prevention unclear									
Piggy-back evaluation									
CDC[11]	NT	WOSCOPS/CARE	Health system	US	10	C = 3; E = 3	DM	$US51 889/LYG	6.8
Published data from RCTs									
Lindholm et al.[26]	PL	WOSCOPS	NM	Sweden	5	C = 5; E = 5	DM	ECU(47 200–803 100)/LYG	5.9
General average of overall score									**5.5**

a After disounting.

$A = Australian dollars; **C** = costs; **CDC** = Centers for Disease Control; **DM** = direct medical; **E** = effects; **ECU** = European Currency Unit; **ICER** = incremental cost-effectiveness ratio; **IDM** = indirect medical; **LIPID** = Long-term Intervention with Pravastatin in Ischaemic Disease; **LIPS** = Lescol Intervention Prevention Study; **LYG** = life-year gained; **NC** = not clear; **NHS** = National Health Service; **NM** = not mentioned; **NT** = no treatment; **NZ** = New Zealand; **PL** = placebo; **PLAC** = Pravastatin Limitation of Atherosclerosis in the Coronary Arteries; **RCT** = randomised controlled trial.

Table II. Average score per question across all economic evaluations

Item[a]	Average score	Minimum score (%)[b]	Maximum score (%)[b]
1. Well defined question in answerable form?	0.76	0	22
2. Comprehensive description of competing alternatives?	0.37	35	9
3. Establishment of effectiveness?	0.18	0	39
4. Identification of costs and consequences?	0.37	22	0
5. Measurement of costs and consequences?	0.82	0	70
6. Valuation of costs and consequences?	0.76	4	39
7. Adjustment for differential timing?	0.59	0	17
8. Incremental analysis?	0.09	91	9
9. Allowance for uncertainty?	0.48	0	0
10. Presentation and discussion of results?	0.63	4	0

a For a detailed description, see Appendix.

b Percentage of articles with a minimum or maximum score on this item (total of sub-items).

2.2 General Characteristics of Included Studies

Most of the studies measured the costs/LYG,[8,9,14-16,18-20,22-27,29] a few measured the costs/QALY gained[11,13,17,21,28,30] or both.[10,12] The publications that measured costs/QALY gained were all published during or after the year 2000.

All the included studies evaluated statins; however, the setting varied over different countries. Studies were conducted in the US,[11,13,17,27,29,30] the UK,[10,14,19,20] Sweden,[16,26,28] Australia,[8,25] The Netherlands,[12] Belgium,[23] Canada,[15] China[21] and Germany,[24] and some studies placed their results in an international setting.[9,18,22]

The included studies contained primary prevention studies[14,23,25,28] and secondary prevention studies,[8-10,13,15,16,18,21,22,27,30] and some combined both.[12,17,19,20,24,29] Two papers did not comment on the type of prevention investigated.[11,26]

Most studies used no treatment or placebo as a comparator; a few did not clearly mention the comparator they used,[19-21,23-25,27,28] and one used usual care as a comparator.[15] Most studies including primary prevention based their effectiveness on data from the WOSCOPS (West of Scotland Coronary Prevention Study) trial.[11,14,19,20,23,25,26,28,29]

The included studies dated from 1996 to 2004. Table I provides additional information.

With the exception of three articles,[10,26,29] most results were published in journals with a medical rather than economic orientation.

2.3 Quality of the Included Studies

The overall score per study varied between 2.7 and 7.7. Table I presents the outcome per study and table II presents the average score per question for all included articles as well as the percentage of included articles with a minimum or maximum score for each question. Not all articles consistently scored positive or negative on the sub-items within a question. For example, when considering question 1, no article had a minimum score on all the sub-items, whereas 22% of the included articles had a maximum score and 78% did not consistently have a minimum or maximum score on the sub-items.

The average quality score of the included studies was 5.5. The average quality scores for articles published in medical- and economics-oriented journals were 5.3 and 6.3, respectively. A trend of improvement for the scores was noticed with time of

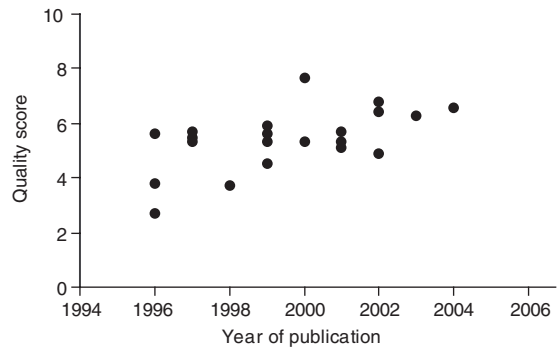

Fig. 1. Trend of quality score over time.

publication (figure 1) [Pearson's R = 0.564, p = 0.005]. When this increase over time is studied for the separate questions we find a statistically significant improvement over time for the identification of costs (question 4) [Pearson's R = 0.550, p = 0.007]. Yet, as shown in table II, the average score for this question was low. Most studies scored high on the measurement of costs and consequences and low on the identification of these costs and consequences and the establishment of effectiveness.

Only two studies[8,11] included a well performed incremental analysis (table II). Furthermore, studies based on piggy-back evaluations tended to have higher quality scores (table I), although not statistically significant (p = 0.257). Piggy-back studies tended to score higher on items 2 and 7 (p = 0.031 and p = 0.046, respectively). For piggy-back studies the alternatives are more clear and better described. This difference is statistically significant. This may be because of the stringent protocols in a trial setting. Additionally, the adjustment for costs and consequences for differential timing seems to be justified better for studies conducted in a piggy-back setting.

3. Discussion

Although this study used inclusion criteria that would assure a minimum quality of the selected studies, we found a disappointing average quality score (5.5). The explanation for most studies scoring low on establishment of effectiveness is that these studies lacked comment on daily practice implications. It was not always clear if and how the study had dealt with the noncompliance occurring in daily practice.

Our findings are consistent with other reviews.[89,90] Similar results are also found in the quality assessment of epidemiological studies.[91,92] This present review shows that, contradictory to expectations,[93] most economic evaluations score well on the measurement and valuation of costs, probably because researchers have a tendency to omit the costs that are difficult to measure and value. Consequently, the reviewed articles had a low score on the identification of costs. Furthermore, several articles did not mention the comparator. We assumed this comparator was doing nothing. It seems that when the comparator is doing nothing, researchers sometimes forget to mention this. Some studies did not adjust for differential timing, did not mention whether discounting was done for effects as well as costs, or state where they derived the discounting rate from. Fewer than half of the studies included well performed sensitivity analyses. Most studies did not discuss the possibilities and difficulties regarding implementation of the preferred programme/treatment. However, the greatest flaw appeared to be that most studies present the cost-effectiveness ratios as incremental cost-effectiveness ratios (ICERs). Table II shows that only two studies presented the ICERs as the incremental benefits for incremental costs incurred.

By reviewing the articles with two reviewers, the results become less 'reviewer-dependent'. Additionally, this is enhanced further by deciding upon disagreement in consensus meetings. Furthermore, the fact that the criteria for the scoring system were established in preliminary meetings (see Appendix) protects the objectivity of both reviewers. Although we did not validate the categorical approach of this scoring system, we have identified another article that also applied a categorical approach to the Drummond checklist.[5]

A limitation of this review was that if the reporting was not accurate and complete, this review evaluated the quality of reporting rather than that of the included studies. We were only able to analyse the information presented in the articles. For example, when study authors commented they were not able to measure all of the identified costs, the studies got a lower score than when no comment was made, because not commenting on the inability to measure identified costs makes it seem as if these costs were measured as well. Another minor limitation is that this review is limited to economic evaluations regarding cholesterol-lowering drugs. For other economic evaluations the quality may be different. Furthermore, long-term data may not be available for other drugs, and decision-makers may need to rely

on short-term studies. However, in the case of lipid-lowering agents the long-term data are abundant.

More recent articles tend to have higher quality scores. This may be the result of an increasing quality demand from the accepting journals over the years. The three articles published in journals with an economic or management background scored above average. The objective of this review was to provide a quality ranking. Nevertheless, differences in settings among studies are equally as important as the quality of the study for those using economic evaluations. For example, differences in healthcare systems among different countries might make it impossible to apply the results of economic evaluations from one country to another.[94] Decision-makers should look not only at the quality of the articles but also at the transferability of the results to their specific population and healthcare system. The articles from van Hout and Simoons[12] and Johannesson[28] meet our inclusion criteria but were aimed at guideline development and may not be useful to decision-makers in determining whether treatment is cost effective for their population.

4. Conclusion

Policymakers who want to use economic evaluations should use those that employed appropriate methodology and produced valid results. In that regard it seems that policymakers are better informed using recent publications, as the quality of studies appears to have increased over time. However, policymakers should remain critical regarding the methodology employed as the overall quality of economic evaluations is disappointing. This review focused on the methodology employed by the studies but policymakers should also consider whether the results are applicable to their own setting.

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Appendix: Scoring Method Based on Drummond's Checklist

The 10 questions are assigned equal weights in determining the overall score. Correspondingly, within one question the sub-items are assigned equal weights. The nature of question 3 means it is impossible to score on several sub-items.

1. **Was a well defined question posed in an answerable form?**

a. If the article examined both costs and effects, the score was 1.00 and if not, the score was 0.00.

b. If the study involved a comparison of alternatives, the score was 1.00 and if not the score was 0.00.

c. If the article stated the viewpoint and placed the study in a decision-making context, the score was 1.00. If the study did only one of the two, the score was 0.50 and if it did neither, the score was 0.00.

2. **Was a comprehensive description of the competing alternatives given?**

a. If the article omitted alternatives important from the stated viewpoint or the policy setting the study was conducted in, the score was 0.00. If there was no viewpoint, policy context or alternative stated, the score was 0.00 because the legitimacy of the choice of the alternatives is based on the viewpoint and policy context. If all the alternatives were included, the score was 1.00, and if it was not clear what the alternatives were, the score was 0.00.

b. If a do-nothing alternative was considered, the score was 1.00. If a do-nothing alternative was not considered but should have been, the score was 0.00 and if it was not necessary to consider this alternative, the score was 1.00. If the article did not clarify the policy context or mention the chosen alternative, the score was 0.00.

3. **Was the effectiveness of the programmes or services established?**

a. If an RCT was conducted or primary data from an RCT were used and allowances were made for regular practice (meaning the effect was adjusted for noncompliance either by assumptions or by using practice data), the score was 1.00. If no allowances were made but the authors clearly described how they derived their effectiveness data, the score was

0.5, and if neither requirement was fulfilled, the score was 0.00.

b. If the effectiveness was established through a meta-analysis or a systematic review of RCTs or obtained through publications concerning a certain trial and allowances were made for regular practice, the score was 1.00. The score was 0.50 if no allowances were made and 0.00 if the effectiveness was not established through a meta-analysis or systematic review of RCTs.

c. If the effectiveness was established through an observational study and the biases were discussed and corrected for as much as possible, the score was 1.00. If the effectiveness was established through an observational study but the potential biases were not discussed, the score was 0.5, and if neither requirement was met, the score was 0.00.

4. **Were all the important and relevant costs and consequences for each alternative established?**

a. If the range was wide enough, the score was 1.00. If the study range was not wide enough for either costs or effects, the score was 0.50, and if the range was not wide enough for costs and effects, the score was 0.00. If the study did not state a research question, aim, viewpoint or policy context, the score was 0.00. When studies only stated the type of costs without identifying these costs, the score was 0.00.

b. If the study covered all the relevant viewpoints (based on the research question), the score was 1.00; if not, the score was 0.00. If the study did not clearly state a research question it was impossible to decide if the range was wide enough; therefore, the score was 0.00.

c. If the identified costs included capital and operating costs, the score was 1.00, and if not, the score was 0.00. When it was unclear whether both types of costs were included, it was assumed they were not and therefore the score was 0.00.

5. **Were costs and consequences measured accurately in appropriate physical units?**

a. If any of the identified items were omitted and the reason was commented on, and this carried no weight in the subsequent analysis, the score was 0.50; without any comment the score was 0.00. If all the items were included, the score was 1.00. If the article did not mention excluded items we assumed that none of these items were excluded.

b. If there were circumstances that made measurement difficult, the score was 1.00 if they were handled appropriately and 0.00 if not or if the article did not explicitly mention how the difficulties were overcome. If there were no special circumstances, the score was 1.00.

6. **Were costs and consequences valued credibly?**

a. If all sources of values were clearly identified, the score was 1.00. When only some of the sources were identified, the score was 0.50, and when none of the sources were identified, the score was 0.00.

b. When market values were employed, the score was 1.00. If not all prices represented market values, the score was 0.50. If no market values were employed, the score was 0.00. If it was unclear for a portion of the values, the score was 0.50. If it was unclear for all values, the score was 0.00.

c. If the study attempted to approximate market values when these were absent or missing, the score was 1.00, and if they did not, or did not comment on this, the score was 0.00. If the study approximated market values but not for all items, or it was unclear for a portion of the values whether they represented market values, the score was 0.50. If the values were not absent, this item was redundant; therefore the score was 1.00. If it was impossible to tell whether this item was redundant, the score was 0.00.

d. When all the consequences were valued appropriately and methodologically sound, the score was 1.00; if only a portion of the consequences were valued appropriately, the score was 0.50; and if none of the items were valued appropriately, the score was 0.00 (i.e. wrong type of analysis used). If the article did not state a research question, viewpoint, aim or policy context of the decision under consideration, the score was 0.00 because the legitimacy of the valuation of the consequences was unclear.

7. **Were costs and consequences adjusted for differential timing?**

a. If both costs and consequences were discounted, the score was 1.00. When only costs or consequences were discounted, the score was 0.50, and when neither was discounted, the score was 0.00.

When it was clear that the study applied the discounting method but unclear whether both costs and effects were discounted, the score was 0.00.

b. When justification was given for both discount rates, the score was 1.00. When justification was given for only one rate, the score was 0.50, and when no justification was given at all, the score was 0.00. If the study did not discount at all, the score was 0.00.

8. **Was an incremental analysis of costs and consequences of alternatives performed?**

a. If the analysis assessed the incremental benefits that were incurred for any incremental costs, the score was 1.00; if not, the score was 0.00. If it was not clear whether the analysis performed was incremental (because of the way it was reported), the score was 0.00.

9. **Was allowance made for uncertainty in the estimates of costs and consequences?**

a. If data on costs or consequences were stochastic and the statistical analysis performed was appropriate, the score was 1.00. If neither were stochastic, the score was 1.00. If the appropriate analysis was not performed, the score was 0.00.

b. If a sensitivity analysis was employed and the article provided justification for the range of values, the score was 1.00. If the article provided no justification or a justification for only a portion of the ranges chosen, the score was 0.50, and when the study did not include a sensitivity analysis at all, the score was 0.00, unless there was no uncertainty in the estimates of costs and consequences. If the study did not perform a sensitivity analysis on all uncertain items, the score was 0.50.

c. If no sensitivity analysis was performed, this item was redundant and the score was 1.00. When a result provided the same conclusion, in the sensitivity analysis, regarding the cost effectiveness of the evaluated items, the score was 1.00, and if not, the score was 0.00.

10. **Did the presentation and discussion of study results include all issues of concern to users?**

a. If the conclusion was based on an overall index (i.e. ICER) and interpreted intelligently, the score was 1.00. If the conclusion was based on a range of cost-utility or cost-effectiveness ratios and the results were interpreted intelligently, the score was 1.00. If the results were interpreted in a mechanistic fashion, the score was 0.00. If it was hard to tell how the results were interpreted, the score was 0.00.

b. If the results were compared with those of others who had investigated the same question and allowances were made for potential differences, the score was 1.00; if no allowances were made after comparison, the score was 0.50. If no comparison was made or the article did not pose a research question, the score was 0.00. If no similar studies were available with which to compare the results and the article mentioned this, the score was 1.00.

c. If the study discussed the generalisability of the results, the score was 1.00; if not, the score was 0.00.

d. If the study took into account considerations other than those derived from the economic evaluation (e.g. organisational aspects), the score was 1.00; if not, the score was 0.00. When studies mentioned these other considerations but did not elaborate on them, the score was 0.00 as well.

e. If the study discussed the possibilities and difficulties regarding implementation of the preferred programme, the score was 1.00; if not, the score was 0.00.

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