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Manuscript Draft

Manuscript Number: EJHE-D-10-00140R1

Title: The use of cost per life year gained as a measurement of cost-effectiveness in Spain. A systematic review of recent publications.

Article Type: Original Research

Keywords: life year gained; quality adjusted life year; economic evaluation; threshold; Spain

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Abstract: Objectives: The objective of this study was to evaluate the methodological characteristics of cost-effectiveness evaluations carried out in Spain since 1990 which include LYG as an outcome to measure the incremental cost-effectiveness ratio.

Methods: A systematic review of published studies was conducted describing their characteristics and methodological quality. We analyze the cost per LYG results in relation with a commonly-accepted Spanish cost effectiveness threshold and the possible relation with the cost per quality adjusted life year (QALY) gained when they were both calculated for the same economic evaluation.

Results: A total of 62 economic evaluations fulfilled the selection criteria, 24 of them including the cost per QALY gained result as well. The methodological quality of the studies was good (55%) or very good (26%). A total of 124 cost per LYG results were obtained with a mean ratio of 49,529€ and a median of 11,490€ (standard deviation of 183,080). Since 2003, a commonly-accepted Spanish threshold has been referenced by 66% of studies. A significant correlation was found between the cost per LYG and cost per QALY gained results (0.89 Spearman-Rho, 0.91 Pearson).

Conclusions: There is an increasing interest for economic healthcare evaluations in Spain and the quality of the studies is also improving. Although a commonly-accepted threshold exists, further information is needed for decision making as well as to identify the relationship between the costs per LYG and per QALY gained.

Response to Reviewers: We decided to give response to specific reviewer and editor comments in this box and uploading the corresponding attachment file as well.

Ref.: Ms. No. EJHE-D-10-00140

The European Journal of Health Economics

Dear Mr. Pérez Alcántara,

Reviewers have now commented on your paper. You will see that they are advising that you revise your

manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

The reviewers' comments can be found at the end of this email or can be accessed by following the provided link.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript.

Your revision is due by 02-03-2011.

To submit a revision, go to <http://ejhe.edmgr.com/> and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely
Wolfgang Greiner
Managing Editor (Editorial Office)
The European Journal of Health Economics

Reviewers' comments:

Reviewer #1:

The manuscript EJHE-D-10-00140 is an interesting contribution to an important methodologic discussion, i.e. outcome measurement within the framework of health economic studies by means of life years gained (LYG) and cost per quality adjusted life year (QALY). The authors conducted a systematic review which aims at assessing the methodological quality of the increasing number of health economic evaluations in Spain and at investigating the relationship between the cost per LYG results and the cost per QALY. An additional analysis focuses on the question whether the recommended cost per LYG threshold published in Spain in 2002 has had an impact on afterwards published health economic evaluations.

In the discussion section (p. 6, line 37f) the authors state that "the number and quality of published Spanish health economic evaluations seems to improve as years go by". In order to support this statement, quality criteria are pointed out in the same paragraph. The authors argue that "in past reviews" certain standards or quality criteria were not sufficiently met. This finding should be described in greater detail in the results section. Is there a break-even point, for instance a specific publication date of a study or a review, which marks the onset of the quality gain in health economic assessments in Spain? Or is it a continuous process of quality improvement? This point should be described more precisely.

RESPONSE:

We now state in the section ICER analysis:

"However, a review by Sacristán et al. in 2002 found that most economic evaluations that recommended the adoption of a certain health intervention were based on ICE lower than 30,000 € per LYG [12]. This commonly-used threshold has been extended to cost per QALY and strengthened by the opinion of expert Spanish health economists [13]." Page 4 line 16

In the Results section we now state:

"Compared to previous systematic Spanish reviews [1,4], some methodological aspects seem to have improved. First, 82% of studies reviewed stated the perspective of the evaluation, compared to 28 and 43%, respectively, in previous reviews [1,4]. Second, the incremental cost and LYG differences are shown together with incremental ratios in 84% of studies. Third, 97% of studies conducted some form of sensitivity analysis, an essential requirement for any good economic evaluation, compared with only 30-68% [1,4] of past reviews. And fourth, although only 47% of studies stated the source of financing, this is greater than the 29% found in past reviews [4]." Page 7, line 21

And:

"As previously stated, a review published in 2002 found that most studies considered technologies with an incremental cost-effectiveness ratio below 30,000€ as efficient [12]. Our review showed that, since 2003, this unofficial threshold has been explicitly used as a reference by 66% of studies included." Page 9, line 10

In the Discussion section we now state:

"Analysis of the methodological quality of the studies published since 2003, showed that 86% (30 of 35) were rated as (code++ or code +), showing the possible influence of previously published reviews in 2002 [1,12] that may have led to greater methodological rigor. Moreover, it should be expected that the recent publication of Spanish recommendations on the economic evaluation of health technologies [11] will reinforce this trend in the future." Page 11, line 6.

END RESPONSE

Another main critique is the following: At first sight, the significant correlation between cost per LYG and cost per QALY seems to be self-evident. Though, this correlation may vary across different types of diseases. The authors, being aware of this aspect, give examples for such as cancer and chronic illness (p. 7, line 46ff). Nevertheless, it is doubtful whether the statistical approach of this study is suitable for differentiating between the various illness conditions. The predominating impression after having read the paper is that the analyses equalize these differences rather than accentuating them.

RESPONSE:

We agree with the reviewer. We have added some points in the Discussion on this issue, and now conclude that:

"Therefore, larger studies where the primary objective is to analyse the relationship between ICE thresholds and types of diseases would be necessary. In the present study, only 9 out of 58 results, corresponding to 4 studies, showed this discrepancy, which is not sufficient to reach any conclusions." Page 13, line 25.

END RESPONSE.

Reviewer #2:

Dear Editor/Dear Authors

The Manuscript Number EJHE-D-10-00140 "The use of cost per life year as cost Effectiveness Gained measure result in Spain. A recent publications review" is an interesting exercise in two complementary dimensions: first, it can provide guidance on the threshold of acceptability implicitly used in Spanish economic evaluation of health interventions, and second, it can provide answers to whether the Spanish authors have accepted the threshold discussed by Sacristán et al in 2002.

In my opinion, the authors commit two conceptual errors that influence the development of the manuscript.

First, Sacristán et al. (2002) did not suggest or advocate that the threshold of acceptability (incremental cost per additional life year gained) should be set at ? 30,000 / LYG. Sacristán et al., reviewed the Spanish papers on economic evaluation of health care interventions published from 1990 to 2000 and analyzed the recommendations of the authors of these works on what is supposed to be worth the incremental cost effectiveness ratio efficiently. Therefore, a part of the work of the authors of the manuscript EJHE-D-10-00140 had already been made by Sacristán et al. (2002).

Secondly, it is wrong to cite that "Later threshold cost per QALY extended to by the Spanish Health Economics Association [13]" The threshold of 30,000 ?/LYG has been never adopted or recognized by the Spanish Health Economics Association in the debate on the need for greater use of economic evaluation studies in healthcare decision making (<http://www.aes.es/Publicaciones/AESEE2.pdf>). The reference 13 is only the opinion of a member of the Spanish Health Economics Association issued individually, not on behalf of the Spanish Health Economics Association.

Therefore, my recommendation is that the manuscript EJHE-D-10-00140 was accepted for publication on condition that (a) the authors should carry out major changes in the manuscript and (b) the authors should focus their aim to respond if the threshold discussed in the work of Sacristán et al (2002) of ? 30,000 / LYG has been adopted as a reference in Spanish papers published in later years (from 2003 until now) or not.

RESPONSE:

We agree with the reviewer that no threshold was suggested either in the paper by Sacristan nor in any statement by the Spanish HEA and have revised the manuscript to emphasize this. We also include new material that addresses the question of whether the threshold suggested by Sacristán el al. have been adopted or has influenced Spanish papers published subsequently.

END RESPONSE.

More specifically:

1) The review of economic evaluation studies carried out between 1990 and 2000 was yet conducted by Sacristán et al. (2002). Authors are encouraged to focus their review in the period following the publication of the work of Sacristán et al., ie the period 2003-2009. The opposite is repeat work already done and published.

RESPONSE:

We agree with the reviewer that, to some extent, we have 'repeated' the review by Sacristán et al (2002), since we cover the period already analyzed in that paper. However, we believe that considering all economic evaluations (including those published before 2002) enabled us to better analyze the evolution of some aspects, such as the methodology quality of the studies or the potential influence of certain key publications like that by Sacristán et al. (2002). It also provides a larger sample size that may help in some of the analyses carried out.

END RESPONSE.

2) It would be interesting to include studies using the QALY as an outcome, since in the Spanish debate on the desirable value of the threshold, the figure of 30,000 euros has been used as a reference of a good value for a QALYs (eg reference 13).

RESPONSE:

A companion study using QALYs has already been carried out by Rodriguez-Barríos et al (2011, in press), the first author of the present study. Since C/LYG is also a commonly used C/E ratio, in this paper we wanted to focus on studies using C/LYG and introduce the comparison between this and C/QALY when both ratios were available (Rodríguez JM, Paz S, Lizan L, González P. The use of Quality Adjusted Life Years (QALYs) in the economic evaluation of health technologies in Spain: a review of the 1990-2009 literature. Value in Health 2011 Volume 14 Issue 4.)

In the Discussion section we now state:

"One limitation of this study is the narrow focus on methodologies using cost per LYG as a result. However, we believe that a detailed examination of this particular topic was desirable, since a similar review focused on the results of studies using cost per QALY has been published elsewhere [5]." Page 11, line 13.

END RESPONSE.

3) The authors should be used as an element to consider whether in the studies reviewed made explicit references to the article of Sacristán et al. (indicating that the authors knew the threshold discussed) and if the authors explicitly compare their results with the threshold discussed by Sacristán et al. (2002). Finally, another item to discuss would be whether the authors' recommendations were based on a comparison of the results of their studies with the threshold of 30,000 per LYG or 30,000 per QALY. In most of the studies cited so it is. And this is a strong argument in favour of the endogenization of the threshold of 30,000 euros in the Spanish framework of the economic evaluation of health care technologies, contrary to what is suggested as a main conclusion of the manuscript.

RESPONSE:

In the Results section we now state:

"As previously stated, a review published in 2002 found that most studies considered technologies with an incremental cost-effectiveness ratio below 30,000€ as efficient [12]. Our review showed that, since 2003, this unofficial threshold has been explicitly used as a reference by 66% of studies included." Page 9, line 10.

In the Discussion section we now state:

"Analysis of the methodological quality of the studies published since 2003, showed that 86% (30 of 35) were rated as (code++ or code +), showing the possible influence of previously published reviews in 2002 [1,12] that may have led to greater methodological rigor. Moreover, it should be expected that the recent publication of Spanish recommendations on the economic evaluation of health technologies [11] will reinforce this trend in the future." Page 11, line 6

And

"Different thresholds have been stated in Spanish publications (ranging from 30,000€ to 50,000€/QALY) [12,21,22], but a recommendation of 30,000€/QALY gained is commonly considered as cost effective for most authors after the review by Sacristán et al. in 2002[12]." Page 12, line 10.

END RESPONSE.

4) It would be necessary to include control variables in the analysis or perform sensitivity analysis: Is it feasible to compare the results and findings of studies where the source of funding is private or where one or several authors works at private companies to the results and conclusions of studies where the source of funding is public or where the authors works at public organizations? Is it possible to compare the results and conclusions of the papers published in journals indexed in the Journal of Citation Report with those who are not?

RESPONSE:

We now state in the Results section:

"Analysis of the cost per LYG of all studies reviewed according to the source of funding showed that robust mean results were quite similar (11,539€ for privately-funded studies, 18,855€ for publicly-funded studies and 13,069€ for studies without the source of funding stated). However, this comparison is biased due to the small number (3) of publicly-funded studies." Page 9, line 4.

We were not able to compare studies appearing in indexed and non-indexed journals because only 19 of the 124 cost per LYG results were from studies published in non-indexed journals.

END RESPONSE.

5) Similarly, the authors should discuss the potential existence of publication bias in the field of economic evaluation when the cost-effectiveness ratio found is very high. The manuscript would benefit from a thorough discussion on this topic.

RESPONSE:

We now state in the Discussion section:

"We found no clear influence of the commonly-used cost per LYG threshold of 30,000€ in studies published after the article by Sacristán et al (2002). However, an increase in the number of studies with cost per LYG results close to, but below, the 30,000€ threshold was found, which might indicate a certain temporary publication bias caused by the implicit acceptance of a threshold of efficiency, although more information would be needed to reach definitive conclusions." Page 12, line 14.

END RESPONSE.

Minor comments:

Authors should review the manuscript and correct some typos.

RESPONSE:

The manuscript has been revised by an English native medical translator.

END RESPONSE.

I would like to stress that if the manuscript is reviewed according to these suggestions, the work will be of great interest not only for Spanish readers, as he delves into a very important issue for European health policy makers as the endogenization of explicit or implicit thresholds of acceptability in the field economic evaluation is.

I hope these comments are useful to the Editor and Authors

Yours sincerely

INTRODUCTION

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2 Economic evaluation provides information to healthcare professionals, decision-makers and consumers in
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4 general about the efficiency (the relation between cost and effects) of health technologies that may aid the
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6 choice of the most-favourable option [1]. Health technology is defined as any kind of drug, device and
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8 medical or surgical procedure used in healthcare management. The development of new health
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10 technologies, whose aim is to improve general health by reducing mortality and morbidity and increasing
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12 the quality of life, involves costs for the society and for healthcare providers [2]. The scarcity of available
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14 resources and the increasing demand for health care requires more- rational assignment of resources and
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16 better definition of priorities: in this scenario, economic evaluation may provide valuable information [3].
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19 Economic evaluation of health technologies has been increasing over recent decades in Spain, as
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21 evidenced by systematic reviews of Spanish economic healthcare evaluations [1,4,5]. However, these
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23 studies also point out some methodological aspects to be improved, including the definition of the
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25 perspective used in the study or the inclusion of sensitivity analyses, among others.
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27 Textbooks and guidelines on health economic evaluation typically distinguish four different types of
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29 evaluation: cost-benefit analysis, cost-utility analysis (CUA), cost-effectiveness analysis (CEA) and cost-
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31 minimization analysis [6]. Each deals with costs but differs in the way the consequences of health care
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33 programs are measured and valued [7]. In cost-benefit analysis, both costs and consequences are
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35 measured in monetary units, while in cost-minimization analysis only costs are measured considering the
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37 same consequences between comparators. In CEA, consequences are measured in natural units (life years,
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39 events prevented, percentage of success) while in CUA, life years are adjusted by quality.
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41 CEA is the most-frequently used type of economic evaluation in Spain, together with CUA [8]. In CEA,
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43 health outcomes are measured in units of effectiveness, frequently disease-specific, which may be
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45 considered as intermediate or final outcomes. When comparing different health technologies using
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47 intermediate outcomes, only the same kind of effectiveness measures and final outcomes, such as life
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49 years gained (LYG), offer relevant information to decision makers.
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52 The objective of this study was to evaluate the methodological characteristics of CEA carried out in Spain
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54 since 1990 which include LYG as an outcome to measure the incremental cost-effectiveness ratio (ICER).
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56 Secondary objectives were first, to determine whether the cost per LYG results were influenced by a
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58 commonly-accepted cost-effectiveness threshold and second, to assess possible differences in study
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1 conclusions where quality adjusted life years (QALY) gained were also reported as an outcome measure
2 together with LYG.
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6 **METHODS**

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9 A systematic review of published studies on the economic evaluation of health technologies in Spain
10 including LYG as an outcome measure was conducted in PubMed/Medline and the CRD database (March
11 2009).
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16 The following combinations of terms were applied to the PubMed/Medline database: ("Cost-Benefit
17 Analysis"[Mesh] OR "Models, Economic"[Mesh] OR "Costs and Cost Analysis"[Mesh] OR
18 "Economics"[Mesh]) AND (Spain OR Spanish) AND (qaly OR avac OR lyg OR avg OR "life saved" OR
19 "life year saved" OR "life gained" OR "vida salvada" OR "año de vida ganado" OR "life year gained" OR
20 "life-years gained" OR "year of extended life"). The systematic review was limited to evaluations
21 involving humans and whose publication language was Spanish or English.
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28 The search strategy for the CRD database combined the following terms: "Spain" AND "cost
29 effectiveness" AND ("life year gained" OR "life year saved") NOT "review".
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33 We searched other relevant local publications by hand, including "Revista Española de Economía de la
34 Salud", "Pharmacoeconomics Spanish Research Articles", "Revista Española de Enfermedades
35 Metabólicas Óseas", "Angiología" or "Vacunas".
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42 **Inclusion and exclusion criteria**

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45 Articles were selected according to the following inclusion criteria, a) studies conducted in the Spanish
46 context; b) studies published in either Spanish or international journals; c) studies related to economic
47 evaluation of health technologies; d) study results had to include a cost-effectiveness analysis expressed
48 in cost per LYG; e) studies referred to either adult or paediatric populations; f) studies conducting an
49 incremental cost-effectiveness analysis.
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55 Studies were excluded if a) they included QALYs and not LYG as an outcome measure; b) study results
56 did not include an incremental cost-effectiveness ratio; c) the study was a systematic review.
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Quality assessment

To assess the methodological quality of articles, a criteria checklist was developed as an adaptation of the criteria checklist for economic evaluations recommended by the National Institute of Health and Clinical Excellence [9], assigning a score of Code (-), Code (+) or Code (++) to value the methodological quality of studies. The criteria suggested by the Oxford Centre for Evidence Based Medicine [10] for economic and decision analysis were also applied to rank the validity of the evidence.

ICER analysis

The ICER is the most frequently-used method of comparing treatment alternatives or clinical pathways in economic evaluations of healthcare. Different healthcare authorities have adopted a maximum ICER threshold to help decide whether a health technology is cost-effective or not and whether it should be adopted by the healthcare system. In Spain, there is no official threshold recommended by healthcare authorities as a “rule-of-thumb” for the economic evaluation of health technologies [11]. However, a review by Sacristán et al. in 2002 found that most economic evaluations that recommended the adoption of a certain health intervention were based on ICER lower than 30,000 € per LYG [12]. This commonly-used threshold has been extended to cost per QALY and strengthened by the opinion of expert Spanish health economists [13]. However, the adoption of a fixed threshold could result in economic studies seeking the maximum price for the technology assessed that still shows a cost-effectiveness ratio below the threshold [14].

Our review also identified studies that calculated cost-effectiveness results in terms of both LYG and QALYs gained in order to determine whether, considering the threshold of 30,000€ per QALY/LYG, they yield the same conclusion or there were differences [15]. The analysis used a dispersion graph comparing cost per LYG and cost per QALY gained in relation to the cost-effectiveness threshold.

The cost-effectiveness results of studies reviewed were updated to 2009 Euros using the inflation rates stated by the National Statistics Institute [16] and the corresponding exchange rates when necessary. In order to normalize the results taking into account biased and asymmetric data, a Box-Cox transformation of cost-effectiveness data using the natural logarithm was carried out [17].

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2 **RESULTS**
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5 Our search yielded a total of 201 references, 62 of which were finally included according to the inclusion
6 and exclusion criteria (Fig.1, table 1).
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11 [Figure 1 Selection process]
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17 The oldest study selected was published in 1993 and the latest was published in March 2009, with 76% of
18 studies being published from 2002 onwards (Fig.2).
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24 [Figure 2, Annual distribution of the studies included]
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29 A total of 58% of studies were published in Spanish journals and 42% in international journals. Four
30 studies were in paediatric populations, four in paediatric and adult populations (vaccination studies) and
31 the remaining 87% in adult patients. Sixty-five percent compared therapeutic interventions while the rest
32 dealt with preventive strategies (four related to screening programs). The studies were conducted for
33 cardiovascular diseases (31%), oncology (23%), infectious diseases (11%), respiratory diseases (11%),
34 smoking (8%), hepatitis (6%), diabetes mellitus (5%) and musculoskeletal disorders (5%).
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39 The most-frequently used perspective was that of the Spanish National Health System (69%). The societal
40 perspective was only used in five studies (in four together with the National Health System perspective).
41 In two articles the authors stated a societal perspective but did not consider indirect costs. The perspective
42 of the evaluation was not stated in 11 articles (18%).
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47 The currency and year for unit values was acknowledged in 81% of studies, and only the currency in the
48 remaining studies. The currencies most-used were the Euro (n=46) followed by the Spanish Peseta (n=8),
49 US Dollar (n=7) and the Ecu (European Currency Unit before 1999) in one study.
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1 necessary and why a specific discount rate was applied. The most-common discount rate used was 3%
2 (42%), followed by 5% (25%), 6% (13%), 3.5% (9%), 4% (one study) and 4.25% (one study). In 89% of
3 studies, the discount rate was the same for costs and health benefits.
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6 The robustness of the results was tested by sensitivity analysis in 97% of studies, with one-way sensitivity
7 analysis being used in 58% of studies, other methods such as multivariate or probabilistic sensitivity
8 analysis together with one-way sensitivity analysis in 19%, multivariate analysis alone in 15% and
9 probabilistic sensitivity analysis alone in 5%.

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11 The ICERs were clearly stated in 84% of studies by calculating the cost and effect differences between
12 the comparators evaluated. In the remaining studies, the incremental cost-effectiveness was stated without
13 showing the differences in costs and effects.
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16 In 74% of studies, the authors acknowledged the limitations of the study. The source of funding was
17 stated in 47% of studies, of which 90% were privately funded. Only three studies were publicly funded,
18 none since 2004.
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21 The level of evidence of 76% of studies was considered as 3b (analysis based on limited alternatives or
22 costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically-sensitive
23 variations) due to the diverse nature of the sources used to estimate costs and effects, and because
24 sensitivity testing relied only on one-way analyses. Ten studies (16%) were assigned a 2b level of
25 evidence (analysis of the effectiveness based on limited review(s) of the clinical evidence or single
26 studies; and including multi-way sensitivity analyses) and five studies (8%) were considered level 4 (no
27 sensitivity analysis included).
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30 The methodological quality was considered to be good (Code +) in 55% of studies, very good (Code ++)
31 in 26% and not good (Code -) in 19%.
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34 Compared to previous systematic Spanish reviews [1,4], some methodological aspects seem to have
35 improved. First, 82% of studies reviewed stated the perspective of the evaluation, compared to 28 and
36 43%, respectively, in previous reviews [1,4]. Second, the incremental cost and LYG differences are
37 shown together with incremental ratios in 84% of studies. Third, 97% of studies conducted some form of
38 sensitivity analysis, an essential requirement for any good economic evaluation, compared with only 30-
39 68% [1,4] of past reviews. And fourth, although only 47% of studies stated the source of financing, this is
40 greater than the 29% found in past reviews [4].
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2 [Table 1 Description of the studies included]
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7 **ICER analysis**
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10 A total of 124 cost per LYG results were obtained from the 62 economic evaluations included in our
11 study. The number of LYG results exceeds the number of studies included due to different sub-analyses
12 of, for example, different time horizons, patient groups or comparators in the same study. Four (3%) LYG
13 results showed a dominant situation for the intervention analyzed (lower costs and greater effectiveness
14 than the alternative compared) while the rest resulted in a mean cost per LYG of 49,529€ and a median of
15 11,490€. The great diversity of the evaluations with respect to pathologies, patients and methodologies
16 resulted in wide dispersion of the results (standard deviation of 183,080). Therefore, more-robust
17 statistical techniques were applied, such as the Huber estimator [18]. The robust mean calculated using
18 the Huber estimator was 12,515€. Where classical statistical techniques fail to cope well with deviations
19 from a standard distribution, robust statistical methods provide tools for statistical problems in which
20 underlying assumptions are inexact. Huber's M-estimator, a generalization of maximum likelihood
21 estimators, allows data to be described with reduced weighting of outliers. The most widely-used
22 weighting factor for Huber's M-estimator is 1.339 (Table 2).
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39 [Table 2. Description of ICER results.]
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44 Analysis of the cost per LYG of all studies reviewed according to the source of funding showed that
45 robust mean results were quite similar (11,539€ for privately-funded studies, 18,855€ for publicly-funded
46 studies and 13,069€ for studies without the source of funding stated). However, this comparison is biased
47 due to the small number (3) of publicly-funded studies.
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52 As previously stated, a review published in 2002 found that most studies considered technologies with an
53 incremental cost-effectiveness ratio below 30,000€ as efficient [12]. Our review showed that, since 2003,
54 this unofficial threshold has been explicitly used as a reference by 66% of studies included.
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[Figure 3. Year of study and cost per LYG results.]

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5 Of the 62 studies with cost per LYG results, 24 also calculated the cost per QALY gained. A total of 58
6 results of cost per LYG and QALY gained were represented in a dispersion graph to analyze whether the
7 two results provided the same conclusions. In 84% of comparisons, the two results yielded the same
8 conclusion, in 40 cases (69%) the results were below the 30,000€ threshold showing the intervention to
9 be cost effective, and in 9 cases (16%) the results were above the threshold. However, in 4 cases (3 from
10 the same study) the cost per LYG was below the 30,000€ threshold whilst the cost per QALY gained was
11 above it. The other 5 cases (3 from the same study) showed the opposite results (Fig. 4).
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[Figure 4. Study of cost per LYG and cost per QALY gained.]

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27 The Spearman-Rho correlation was used to correlate the estimate between the quantitative characteristics
28 of the cost per LYG and cost per QALY gained. This rank-correlation method is considered robust
29 against outliers and non-normal data distribution. The Spearman rank correlation between the two cost-
30 effectiveness results was 0.89 ($p < 0.001$). After log transformation, the Pearson correlation was used, with
31 a result of 0.91 ($p < 0.001$).
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40 DISCUSSION

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43 Interest in economic evaluations in health care and their contribution to decision making has increased in
44 Spain in recent years [1,4,12]. We conducted a review of economic evaluations of health technologies in
45 Spain assessing the incremental cost per LYG as an outcome from 1993 until the beginning of 2009. The
46 number of publications found reflects this increasing interest.
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51 Of the studies reviewed, only one assessed the cost per LYG for a medical device, with the remaining
52 articles assessing mainly drugs or healthcare programs. As medical devices are used to provide
53 symptomatic improvement, the number of QALY gained is the preferred assessment outcome.
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1 The methodology used by the majority of studies assessed satisfied most of the general methodological
2 aspects considered to represent good practice in international recommendations [3,8,9,10,11]. Compared
3 with previous reviews [1,4] the number and quality of published Spanish health economic evaluations
4 seems to have improved over times, and some deficiencies found in previous reviews seem to have been
5 solved. Analysis of the methodological quality of the studies published since 2003, showed that 86% (30
6 out of 35) were rated as (code++ or code +), showing the possible influence of previously published
7 reviews in 2002 [1,12] that may have led to greater methodological rigor. Moreover, it should be expected
8 that the recent publication of Spanish recommendations on the economic evaluation of health
9 technologies [11] will reinforce this trend in the future.

10 One limitation of this study is the narrow focus on methodologies using cost per LYG as a result.
11 However, we believe that a detailed examination of this particular topic was desirable, since a similar
12 review focused on the results of studies using cost per QALY has been published elsewhere [5]. In
13 addition, despite a comprehensive search, some of the earliest publications may have been overlooked,
14 although their inclusion would have been unlikely to alter the reported findings.

15 Some problems arise in the increasing use of cost-effectiveness thresholds as an explicit decision-making
16 rule. Cost-effectiveness thresholds may vary according to the country or geographical area; in fact, the
17 World Health Organization recommends adjustment by the corresponding gross domestic product [19].
18 They may also vary according to the decision maker (social or health provider perspective), the healthcare
19 technologies compared (preventive or therapeutic), the effectiveness measure of the evaluation chosen
20 (LYG, QALY gained, intermediate clinical outputs) or the disease under study. As an example, recent
21 supplementary advice for appraising life-extending, end-of-life treatments made by NICE [20] recognized
22 the need for further appraisal when the treatment involved is indicated for small populations with
23 incurable illnesses and the most-plausible reference case point estimate for the ICER exceeds the upper
24 threshold of the range normally considered.

25 Cost-effectiveness thresholds are not gathered unanimously in the different international guidelines for
26 health economic evaluation, and the latest Spanish recommendations [11] do not state any explicit
27 thresholds, in contrast with NICE guidelines (25,000-35,000€/QALY gained)[9]. Different thresholds
28 have been stated in Spanish publications (ranging from 30,000€ to 50,000€/QALY) [12,21,22], but a
29 recommendation of 30,000€/QALY gained is commonly considered as cost effective for most authors
30 after the review by Sacristán et al. in 2002[12].

1 We found no clear influence of the commonly-used cost per LYG threshold of 30,000€ in studies
2 published after the article by Sacristán et al (2002). However, an increase in the number of studies with
3 cost per LYG results close to, but below, the 30,000€ threshold was found, which might indicate a certain
4 temporary publication bias caused by the implicit acceptance of a threshold of efficiency, although more
5 information would be needed to reach definitive conclusions.
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10 Other decision sources, such as the potential financial consequences of a new healthcare technology, are
11 not covered by cost-effectiveness thresholds and represent an essential part of a comprehensive economic
12 assessment of a healthcare technology. Budget impact analysis is used to quantitatively estimate the
13 foreseen changes in healthcare expenses for treatment of a specific pathology when an alternative
14 intervention is introduced [23,24], complementing the information provided by the cost-effectiveness
15 results of the new intervention.
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23 When two types of final outcome results are studied (LYG and QALY gained) in the same health
24 economic evaluation, the conclusions of the study do not depend on the final outcome chosen in most of
25 the cases, i.e., the cost per LYG and the cost per QALY gained result led to the same conclusion. The
26 high correlation found in our study between the two ratios (0.89 Spearman and 0.91 Pearson correlation)
27 is similar to that found by Chapman in 2004 (0.86 Spearman and 0.84 Pearson correlation) [15]. This is
28 important because it is often difficult and costly to find utility data for QALY calculation. However,
29 further assessment would be needed to accept this as a fact, and it should be noted that this correlation
30 may vary between different types of diseases. In some cases, choosing LYG or QALY as the outcome of
31 the study may change the cost-effectiveness results of an evaluation. An intervention could be cost-
32 effective considering cost per LYG rather than cost per QALY gained when it involves a better survival
33 outcome but has less quality of life effectiveness (for example, having more side effects, disease
34 complications, survival rates in a severe health state). This would be the case for certain cancers, where
35 life years are gained when disease severity is associated with low levels of quality of life (for example
36 breast cancer in the studies reviewed [25]). The opposite could occur in an intervention in which the
37 quality of life is greatly improved but there is a limited improvement in survival. This would be the case
38 for chronic pathologies with good life expectancy but which are highly-sensitive to quality of life changes
39 associated with improvements related to a new treatment option resulting in fewer disease complications
40 or side effects, such as hepatitis C [26] or type 2 diabetes [27]. Therefore, larger studies where the
41 primary objective is to analyse the relationship between ICER thresholds and types of diseases would be
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necessary. In the present study, only 9 out of 58 results, corresponding to 4 studies, showed this discrepancy, which is not sufficient to reach any conclusions.

Cost-effectiveness analysis is useful in allowing decision makers to maximize resource allocation. Although different approaches have been used to present results (LYG, QALYs, etc), the best alternative may depend on the scope of the study, the disease evaluated and the financial impact of the technologies under evaluation, among other factors.

Our results suggest that some aspects should be improved in future studies using LYG as an effectiveness outcome: a) a clear definition of the perspective of the economic evaluation; b) a description of ICER in all economic evaluations performed, and c) greater use of probabilistic sensitivity analysis to better evaluate uncertainty.

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7 **Tables and figures**

8 Table 1: Description of the studies included
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Reference	Objective	Type of evaluation	Type of intervention	Results	Quality NICE ^a	Quality CEBM ^b
Cairols-Castellote MA, 2009 [28]	To assess the cost-effectiveness of endovascular treatment for the treatment of abdominal aortic aneurysm with respect to open surgery.	CEA-CUA	Therapeutic device	<ul style="list-style-type: none"> ▪ 19,852€/LYG (4 years) ▪ 27,077€/QALY (4 years) ▪ 111,064€/LYG (1 year) ▪ 137,206€/QALY (1 year) 	Code +	2b
Martín-Jiménez M, 2009 [29]	Cost-effectiveness analysis of docetaxel vs. 5-fluorouracil in combined therapy in the initial phases of breast cancer	CEA - CUA	Therapeutic	<ul style="list-style-type: none"> ▪ 2,545€/LYG ▪ 2,855€/QALY 	Code +	3b
Oliva J, 2009 [30]	To assess the cost-effectiveness of a genetic screening program for first-degree relatives of patients with familial hypercholesterolemia compared with the alternative of no screening.	CEA	Preventive (screening)	<ul style="list-style-type: none"> ▪ 3,714€/LYG 	Code ++	2b
Alonso R, 2008 [31]	To evaluate the cost-effectiveness of different preventive strategies in familial hypercholesterolemia in comparison with routine practice: Atorvastatin monotherapy (40 mg or 80 mg), atorvastatin combined with ezetimibe 10 mg (A40+E10 or A80+E10)	CEA	Preventive	<ul style="list-style-type: none"> ▪ 3,268€/LYG (Atorvastatin 40mg vs Clinical practice) ▪ 5,697€/LYG (Atorvastatin 40mg+Ezetimibe 10mg vs Clinical practice) ▪ 1,976€/LYG (Atorvastatin 80mg vs Clinical Practice) ▪ 4,363€/LYG (Atorvastatin 80mg+Ezetimibe10mg vs Clinical Practice) 	Code +	3b
Fernández de Bobadilla J, 2008 [32]	To analyse the efficiency of varenicline compared with bupropion, nicotine replacement therapy and no pharmacological treatment.	CEA – CUA	Therapeutic	Dominant	Code ++	3b
Grupo de	Cost-effectiveness of maintenance	CEA-CUA	Therapeutic	<ul style="list-style-type: none"> ▪ 8,974€/LYG 	Code ++	3b

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Farmacoeconomía del Linfoma Folicular, 2008 [33]	treatment with rituximab compared to no medication in resistant or recurrent follicular lymphoma patients.			<ul style="list-style-type: none"> 9,888€/QALY 		
Largeron N, 2008 [34]	To assess the health and economic impact of implementing a four-valent HPV vaccine alongside existing screening versus screening alone.	CEA-CUA	Preventive	<ul style="list-style-type: none"> 9,147€/LYG 6,860€/QALY 	Code +	3b
Maroto P, 2008 [35]	To evaluate the cost-effectiveness of sorafenib plus best supportive care (BSC) versus BSC alone in advanced renal cell carcinoma.	CEA	Therapeutic	<ul style="list-style-type: none"> 22,850€/LYG (Lifetime) 166,113€/QALY (1 year) 	Code +	3b
Mayordomo J, 2008 [36]	To evaluate the cost-effectiveness of pegfilgrastim 6 mg compared with filgrastim in 45-year-old women with stage II breast cancer in the primary prophylaxis of febrile neutropenia.	CEA-CUA	Preventive	<ul style="list-style-type: none"> 13,365€/LYG 14,128€/QALY 	Code +	3b
Paz-Ares L, 2008 [37]	To assess the cost-effectiveness of sunitinib vs best supportive care in patients with metastatic and/or unresectable gastrointestinal stroma tumours as a second-line treatment.	CEA-CUA	Therapeutic	<ul style="list-style-type: none"> 30,665€/LYG 49,777€/QALY 	Code +	3b
Aballéa S, 2007 [38]	The impact of an increase in vaccination uptake, from the current level to a similar level as that currently achieved in people aged over 65, on costs and on health outcomes.	CEA-CUA	Preventive	<ul style="list-style-type: none"> 10,950€/LYG (SNHS perspective) 16,788€/QALY (SNHS perspective) 3,045€/LYG (societal perspective) 4,669€/QALY (societal perspective) 	Code +	3b
Badía X, 2007 [39]	To analyze the cost-effectiveness of enfuvirtide plus optimized therapy in HIV patients.	CEA	Therapeutic	<ul style="list-style-type: none"> 29,127€/LYG 	Code ++	2b

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Casado MA, 2007 [40]	Cost-effectiveness analysis of first line therapy in patients with metastatic colorectal cancer.	CEA	Therapeutic	<ul style="list-style-type: none"> 157,565€/LYG 	Code +	2b
Fernández de Bobadilla J, 2007 [41]	To assess the cost-effectiveness of atorvastatin 10mg vs placebo using data from the ASCOT lipid-lowering arm.	CEA	Therapeutic	<ul style="list-style-type: none"> 11,614€/LYG 	Code ++	2b
Lázaro P, 2007 [42]	To evaluate the cost-effectiveness of palivizumab in preventing respiratory syncytial virus infection in high risk children.	CEA-CUA	Preventive	<ul style="list-style-type: none"> All children : 19,945€/LYG and 14,630€/QALY Premature infants: 17,609€/LYG and 12,899€/QALY Infants with chronic disease: 25,352€/LYG and 18,617€/QALY 	Code ++	3b
López JM, 2007 [43]	Economic evaluation of use of the tetravalent vaccine in cancer prevention.	CEA	Preventive	<ul style="list-style-type: none"> 5,724€/LYG 	Code +	3b
Piñol C, 2007 [44]	To assess the cost-effectiveness of the addition of acarbose to existing treatment in patients with type 2 diabetes mellitus.	CEA-CUA	Therapeutic	<ul style="list-style-type: none"> 2,253€/LYG 2,475€/QALY 	Code +	3b
Cornuz J, 2006 [45]	To estimate the incremental cost-effectiveness of first-line pharmacotherapies for smoking cessation.	CEA	Therapeutic	<ul style="list-style-type: none"> Gum vs Physician Counselling: 4,247€/LYG and 2,810€/QALY Patch vs Physician Counselling: 3,348€/LYG and 2,216€/QALY Spray vs Physician Counselling: 3,684€/LYG and 2,439€/QALY Bupropion vs Physician Counselling: 1,671€/LYG and 1,107€/QALY 	Code -	3b
Fernández de Bobadilla J, 2006 [46]	To estimate the incremental cost-effectiveness of atorvastatin 50mg versus pravastatin 40mg based on the PROVE-IT trial.	CEA	Therapeutic	<ul style="list-style-type: none"> 321€/LYG 	Code ++	3b

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Fernández de Bobadilla J, 2006 [47]	To perform a cost-effectiveness analysis of the use of Atorvastatin 10mg in the primary prevention of cardiovascular disease in patients with type 2 Diabetes Mellitus.	CEA-CUA	Therapeutic	<ul style="list-style-type: none"> ▪ 6,624€/LYG ▪ 9,054€/QALY 	Code +	3b
Gil JM, 2006 [25]	To compare the efficiency of adjuvant therapy with aromatase inhibitors or with tamoxifen in postmenopausal women with operable breast cancer and positive estrogen receptors.	CEA-CUA	Therapeutic	<ul style="list-style-type: none"> ▪ Exemestane vs tamoxifen (study 2004, 10 years): 36,575€/LYG and 57,165€/QALY ▪ Exemestane vs tamoxifen (study 2005, 10 years): 44,949€/LYG and 70,354€/QALY ▪ Anastrozole vs tamoxifen (10 years): 73,494€/LYG and 117,334€/QALY ▪ Letrozole vs Placebo 10 years): 64,284€/LYG and 102,635€/QALY ▪ Exemestane vs tamoxifen (study 2004, 20 years): 17,518€/LYG and 32,463€/QALY ▪ Exemestane vs tamoxifen (study 2005, 20 years): 21,526€/LYG and 39,802€/QALY ▪ Anastrozole vs tamoxifen (20 years): 37,451€/LYG and 70,303€/QALY ▪ Letrozole vs Placebo (20 years): 29,345€/LYG and 55,656€/QALY 	Code ++	3b
Lamotte M, 2006 [48]	To investigate the health economic implications of using low-dose aspirin in the primary prevention of cardiovascular disease.	CEA-CUA	Preventive	Dominant	Code +	3b
Lázaro y de Mercado P, 2006 [49]	To evaluate the cost-effectiveness of palivizumab in preventing severe respiratory syncytial virus infection in premature infants with a gestational age of	CEA-CUA	Preventive	<ul style="list-style-type: none"> ▪ 18,023€/LYG (SNHS perspective) ▪ 15,028€/QALY (SNHS perspective) ▪ 5,994€/LYG (societal perspective) ▪ 4,997€/QALY (societal perspective) 	Code ++	2b

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	32-35 weeks and 2 or more risk factors.					
Lenne X, 2006 [50]	To evaluate the epidemiological and socio-economic consequences of a routine childhood vaccination program with varicella vaccine.	CEA	Preventive	<ul style="list-style-type: none"> ▪ Vaccine program: 4,481€/LYG (SNHS perspective) and 1€/LYG (societal perspective), ▪ Vaccine program+catch-up: 14,480€/LYG (SNHS perspective) and 9,720€/LYG (societal perspective) 	Code ++	3b
Shearer AT, 2006 [27]	Cost-effectiveness and lifetime diabetes consequences of rosiglitazone in combination with metformin compared to metformin + sulfonyleureas or metformin + bedtime insulin	CEA-CUA	Therapeutic	<ul style="list-style-type: none"> ▪ Rosiglitazone+metformin vs metformin+sulfonyleureas: 28,308€/LYG and 19,560€/QALY in overweight; 32,443€/LYG and 28,021€/QALY in obese, ▪ Rosiglitazone+metformin vs metformin+bedtime insulin: 30,036€/LYG and 11,209€/QALY in overweight; 35,583€/LYG and 13,316€/QALY in obese 	Code +	3b
Badia X, 2005 [51]	To carry out a cost-effectiveness analysis of administering clopidogrel in addition to standard therapy during the first year of treatment in patients with acute coronary syndrome but without ST-segment elevation.	CEA	Preventive	<ul style="list-style-type: none"> ▪ 9,444€/LYG 	Code ++	3b
Buti M, 2005 [52]	To estimate the future morbidity, mortality and costs of treatment with peginterferon alpha-2b plus ribavirin of chronic hepatitis C virus infection.	CEA	Therapeutic	<ul style="list-style-type: none"> ▪ Peginterferon alpha 2b+ribavirin vs No Treatment (29 year old patients): 6,850€/LYG ▪ Peginterferon alpha 2b+ribavirin vs No Treatment (59 year old patients): 10,027€/LYG 	Code +	3b
Cannata J, 2005 [53]	To carry out an economic assessment of Protelos in comparison with placebo to determine its cost-effectiveness profile in	CEA-CUA	Therapeutic	<ul style="list-style-type: none"> ▪ 21,606€/LYG ▪ 33,895€/QALY 	Code -	4

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	the treatment of osteoporosis.					
Grau S, 2005 [54]	To assess the cost-effectiveness of linezolid versus vancomycin for the treatment of ventilator associated pneumonia.	CEA-CUA	Therapeutic	<ul style="list-style-type: none"> ▪ Linezolid vs vancomycin: 1,743€/LYG and 2,095€/QALY, ▪ Linezolid vs vancomycin (Gram positive): 961€/LYG and 1,158€/QALY, ▪ Linezolid vs vancomycin (S. Aureus): 1,109€/LYG and 1,334€/QALY, ▪ Linezolid vs vancomycin (methicillin resistant S.Aureus): 337€/LYG and 405€/QALY 	Code +	3b
Asensi F, 2004 [55]	Evaluate the health outcomes, costs, and cost-effectiveness of vaccination with PCV-7, compared with no vaccination for children.	CEA	Preventive	<ul style="list-style-type: none"> ▪ 26,189€/LYG 	Code +	3b
Balmaña J, 2004 [56]	To analyze the benefits and costs of a surveillance program to identify individuals at risk for hereditary breast and ovarian cancer and offer them genetic testing and a screening program.	CEA	Preventive (screening)	<ul style="list-style-type: none"> ▪ 4,987€/LYG 	Code -	3b
Brosa M, 2004 [57]	To analyse the efficiency of hyperlipidemia management using atorvastatin versus usual care in patients with coronary heart disease using data from the GREACE study.	CEA	Therapeutic	<ul style="list-style-type: none"> ▪ 5,558€/LYG 	Code ++	2b
Camacho J, 2004 [58]	Cost-effectiveness analysis of preventing a transfusion pathogen with Advate.	CEA	Preventive	<ul style="list-style-type: none"> ▪ 22,124€/LYG 	Code -	4
Cook JR, 2004 [59]	To project the lifetime benefit and cost of alternative lipid-lowering treatment strategies for coronary heart disease (CHD) and non-CHD diabetic patients.	CEA	Therapeutic	<ul style="list-style-type: none"> ▪ Prior to CHD : 19,742 – 30,193€/LYG ▪ Diabetic patients non-CHD : 32,516 – 55,741€/LYG 	Code -	3b

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Sacristán JA, 2004 [60]	To assess the cost-effectiveness of drotrecogin alpha (activated) versus that of standard care in the treatment of severe sepsis.	CEA	Therapeutic	<ul style="list-style-type: none"> ▪ 16,787€/LYG 	Code +	3b
Antoñanzas F, 2003 [61]	To assess the efficiency of three smoking cessation strategies based on pharmacotherapies.	CEA	Therapeutic	<ul style="list-style-type: none"> ▪ Bupropion vs physician advice: 3,652€/LYG ▪ Patches vs physician advice: 1,888€/LYG ▪ Gum vs physician advice: 4,885€/LYG 	Code -	3b
Buti M, 2003 [62]	To evaluate the cost-utility of peginterferon alfa-2b plus ribavirin for chronic hepatitis C patients.	CEA-CUA	Therapeutic	<ul style="list-style-type: none"> ▪ Peginterferon+Ribavirin800 vs interferon: 7,292€/LYG and 3,265€/QALY, ▪ Peginterferon+Ribavirin adjusted to body weight vs Peginterferon+Ribavirin800: 5,425€/LYG and 2,291€/QALY ▪ Peginterferon+Ribavirin adjusted to body weight+compliance vs Peginterferon+Ribavirin800: Dominant 	Code -	3b
Gambús G, 2003 [63]	Cost-effectiveness evaluation of fluvastatin 80 mg/day in coronary heart disease.	CEA-CUA	Therapeutic	<ul style="list-style-type: none"> ▪ 17,081€/LYG ▪ 16,403€/QALY 	Code -	4
Moreno A, 2003 [64]	To perform a cost-effectiveness analysis on the use of celecoxib versus traditional non-steroidal anti-inflammatory drugs in the treatment of osteoarthritis.	CEA	Therapeutic	<ul style="list-style-type: none"> ▪ 9,932€/LYG 	Code +	3b
Nuijten MJ, 2003 [65]	Cost-effectiveness of thromboprophylaxis with enoxaparin versus no thromboprophylaxis in patients with acute medical illness.	CEA	Preventive	<ul style="list-style-type: none"> ▪ 85€/LYG 	Code +	3b

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San Miguel R, 2003 [66]	To develop a cost-effectiveness analysis of therapeutic regimens with interferon-alpha and ribavirin in previous interferon non-responders.	CEA-CUA	Therapeutic	<ul style="list-style-type: none"> ▪ Interferon mono 6 months vs No treatment: 24,792€/LYG and 13,223€/QALY ▪ Combo+standard doses of interferon 6 months vs No treatment: 11,662€/LYG and 6,079€/QALY ▪ Combo+high doses of interferon 6 months vs No treatment: 11,507€/LYG and 5,963€/QALY ▪ Combo+standard doses of interferon 12 months vs No treatment: 14,578€/LYG and 7,524€/QALY 	Code +	3b
Hart WM, 2002 [67]	To assess a cost-effectiveness analysis of the treatment of post-menopausal osteoporosis with risedronate and once-a-week alendronate.	CEA-CUA	Therapeutic	<ul style="list-style-type: none"> ▪ Risedronate vs alendronate: Dominant ▪ Risedronate vs no treatment: 301,351€/LYG and 80,807€/QALY ▪ Alendronate vs no treatment: 625,372€/LYG and 114,290€/QALY 	Code +	3b
Hart WM, 2002 [68]	To calculate the cost-effectiveness of adding ramipril to the regular treatment of patients at high risk of suffering cardiovascular events.	CEA	Therapeutic	<ul style="list-style-type: none"> ▪ 13,146€/LYG 	Code ++	3b
Hart WM, 2002 [69]	To estimate the cost-effectiveness of adding ramipril to conventional treatment in patients with heart failure after myocardial infarction.	CEA	Therapeutic	<ul style="list-style-type: none"> ▪ 1,973€/LYG 	Code +	2b
Lindgren P, 2002 [70]	To investigate the cost effectiveness of exemestane compared to megestrol in post-menopausal women after tamoxifen failure.	CEA	Therapeutic	<ul style="list-style-type: none"> ▪ 10,330€/LYG 	Code +	3b
Llovet JM, 2002 [71]	To assess the cost-effectiveness of adjuvant therapy while waiting for liver	CEA	Therapeutic	<ul style="list-style-type: none"> ▪ Surgical resection vs standard management: 49,665 – 86,913€/LYG 	Code +	2b

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	transplantation in cirrhotic patients with early hepatocellular carcinoma.			<ul style="list-style-type: none"> ▪ Percutaneous ethanol injection vs standard management: 24,832€/LYG 		
Plans P, 2002 [72]	To evaluate the cost-effectiveness of pneumococcal vaccination strategies (23 serotypes) in the population aged 5 years and older.	CEA	Preventive	<ul style="list-style-type: none"> ▪ 12,712€/LYG 	Code +	3b
Antoñanzas FA, 2001 [73]	To measure the cost per year of life saved in patients treated with eptifibatid using the PURSUIT trial.	CEA	Therapeutic	<ul style="list-style-type: none"> ▪ 12,712€/LYG 	Code -	4
Soto Alvarez J, 2001 [74]	To assess the efficiency of using spironolactone in the treatment of chronic heart failure when compared with the use of conventional treatment alone.	CEA	Therapeutic	<ul style="list-style-type: none"> ▪ 4,524€/LYG 	Code +	3b
Buti M, 2000 [26]	To determine if the incremental sustained response rate of combination therapy is sufficient to outweigh its extra cost in naive patients with histological mild or moderate chronic hepatitis C.	CEA-CUA	Therapeutic	<ul style="list-style-type: none"> ▪ Moderate CHC combo 12 months vs interferon 12 months (30 years old): 1,198€/LYG and 787€/QALY ▪ Moderate CHC combo 12 months vs interferon 12 months (60 years old): 10,314€/LYG and 3,928€/QALY ▪ Moderate CHC combo 12 months vs interferon 6 months (30 years old): 2,850€/LYG and 1,871€/QALY ▪ Moderate CHC combo 12 months vs interferon 6 months (60 years old): 19,813€/LYG and 7,546€/QALY ▪ Mild CHC combo 12 months vs interferon 12 months (30 years old): 4,063€/LYG and 1,804€/QALY ▪ Mild CHC combo 12 months vs interferon 12 months (60 years old): 49,250€/LYG and 7,599€/QALY 	Code ++	3b

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				<ul style="list-style-type: none"> ▪ Mild CHC combo 12 months vs interferon 6 months (30 years old): 7,982€/LYG and 3,544€/QALY ▪ Mild CHC combo 12 months vs interferon 6 months (60 years old): 87,714€/LYG and 13,533€/QALY 		
González-Larriba JL, 2000 [75]	To analyse the cost-effectiveness ratio of adjuvant therapy with interferon alpha-2b in melanoma patients versus an untreated control group.	CEA	Therapeutic	<ul style="list-style-type: none"> ▪ 11,473€/LYG 	Code ++	3b
Berger K, 1998 [76]	To determine the cost structure of treating advanced ovarian cancer and to determine the cost-effectiveness of paclitaxel and cisplatin as first line chemotherapy.	CEA	Therapeutic	<ul style="list-style-type: none"> ▪ 14,958€/LYG 	Code -	3b
Comas A, 1998 [77]	To study the cost-effectiveness of simple anti-smoking advice in primary care.	CEA	Therapeutic	<ul style="list-style-type: none"> ▪ Women: 1,016 – 1,205€/LYG ▪ Men: 591 – 784€/LYG 	Code +	3b
Plans-Rubió P, 1998 [78]	To assess the cost-effectiveness of treatments for the primary prevention of coronary heart disease.	CEA	Preventive	<ul style="list-style-type: none"> ▪ Smoking cessation vs no primary prevention: 2,848 – 8,800€/LYG ▪ Hypertension treatment vs no primary prevention: 7,711 – 138,678€/LYG ▪ Hypercholesterol treatment vs no primary prevention: 16,912 – 1,844,481€/LYG ▪ Cholesterol diet vs no primary prevention: 13,969 – 162,983€/LYG 	Code +	3b
Plans-Rubió P, 1998 [79]	To assess the cost-effectiveness of available cardiovascular disease prevention programs in Spain.	CEA	Preventive	Treating hypercholesterolemia with lovastatin and hypertension with hydrochlorothiazide, propranolol and nifedipine are the most efficient options,	Code -	4

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Garuz R, 1997 [80]	To perform a cost effectiveness analysis of a breast cancer mammography screening programme.	CEA	Preventive (screening)	<ul style="list-style-type: none"> ▪ 2,990€/LYG 	Code +	3b
Rubió P P, 1997 [81]	To assess the cost-effectiveness of a dietary treatment of hypercholesterolemia.	CEA	Therapeutic	<ul style="list-style-type: none"> ▪ Dietary vs no dietary in men: 7,111 – 69,675€/LYG ▪ Dietary vs no dietary in women: 31,829 – 194,442€/LYG 	Code -	3b
Plans P, 1996 [82]	To assess the cost-effectiveness of early diagnosis breast cancer.	CEA-CUA	Preventive (screening)	<ul style="list-style-type: none"> ▪ 7,038€/LYG and 7,819€/QALY 	Code +	3b
Plans P, 1995 [83]	To calculate the cost-effectiveness of different smoking cessation methods.	CEA	Therapeutic	<ul style="list-style-type: none"> ▪ Medical advice+gum vs medical advice alone: 4,387 – 10,724€/LYG ▪ Medical advice+patch vs medical advice alone: 5,333 – 12,681€/LYG ▪ Medical advice+patch vs medical advice+gum: 5,988 – 14,638€/LYG 	Code +	3b
Plans Rubió P, 1995 [84]	To assess the cost-effectiveness of pneumococcal vaccination of people aged 5 years or more.	CEA-CUA	Preventive	<ul style="list-style-type: none"> ▪ 8,314€/LYG and 4,322€/QALY 	Code +	3b
Plans Rubió P, 1995 [85]	To estimate the cost-effectiveness of hypolipemiant treatment.	CEA	Therapeutic	<ul style="list-style-type: none"> ▪ 33,766 – 469,791€/LYG 	Code +	3b
Badía X, 1993 [86]	To determine the cost-efficacy analysis of treatment with antiendotoxin monoclonal antibodies (HA-1A) in adult patients admitted to intensive care units.	CEA	Therapeutic	<ul style="list-style-type: none"> ▪ All sepsis: 10,861€/LYG ▪ Septic shock: 3,714€/LYG 	Code -	3b

A Code -, + or ++ score was assigned to the methodological quality of the study according to the nature of the sources used; the clarity and comprehensiveness of the information presented; the details given on the economic analysis, the alternatives being assessed and the context in which the technology would be applied.

^a NICE: National Institute for Health and Clinical Excellence

^b CEBM: Oxford Centre for Evidence Based Medicine

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Table 2. Description of the ICER results.

Total cost per LYG cases	124
Dominant cases	4
Non dominant cost per LYG cases (n=120)	
Mean cost	49,529€
Standard deviation	183,080
Median	11,490€
Minimum	85€
Maximum	1,844,481€
Robust mean	
M-estimator (Huber)	12,515€

Figure 1. Selection process

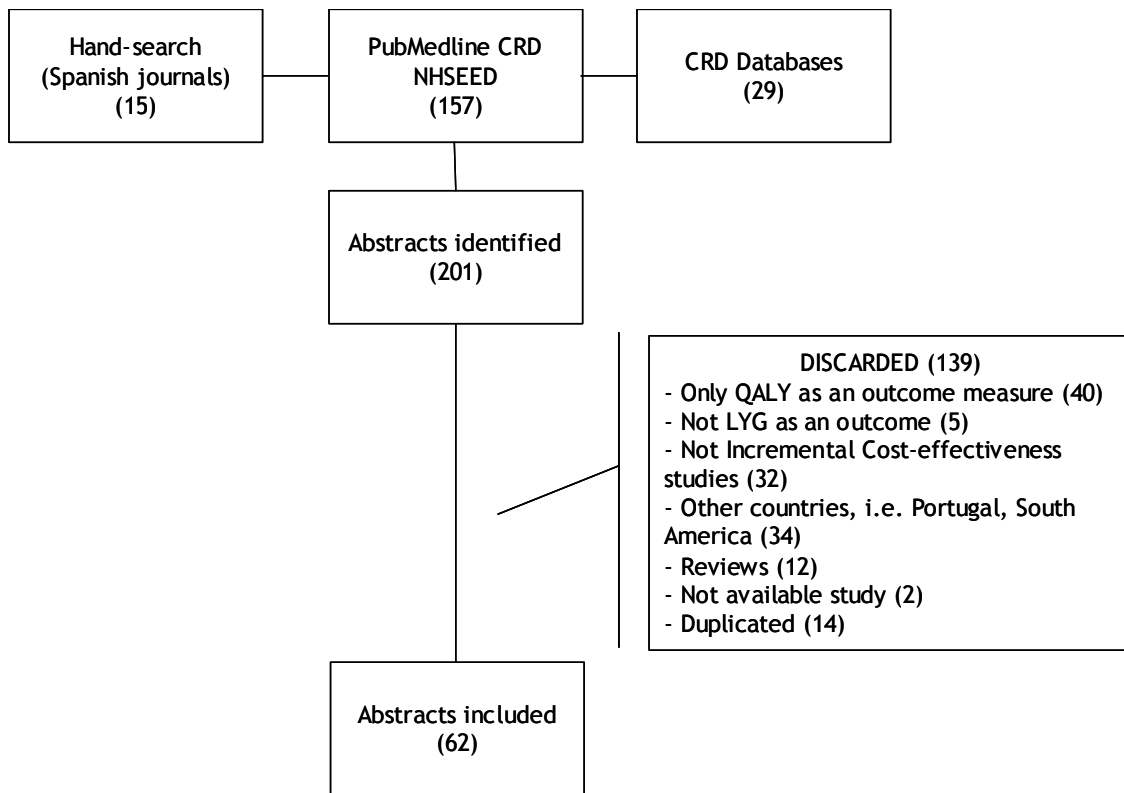


Figure 2. Annual distribution of the studies included

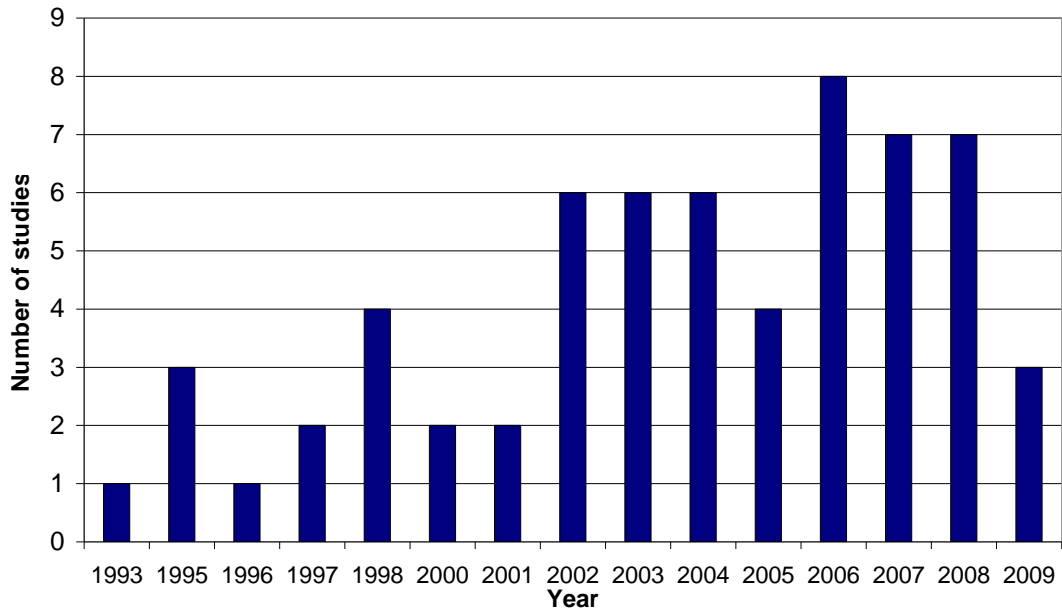


Figure 3. Year of study and cost per LYG results.

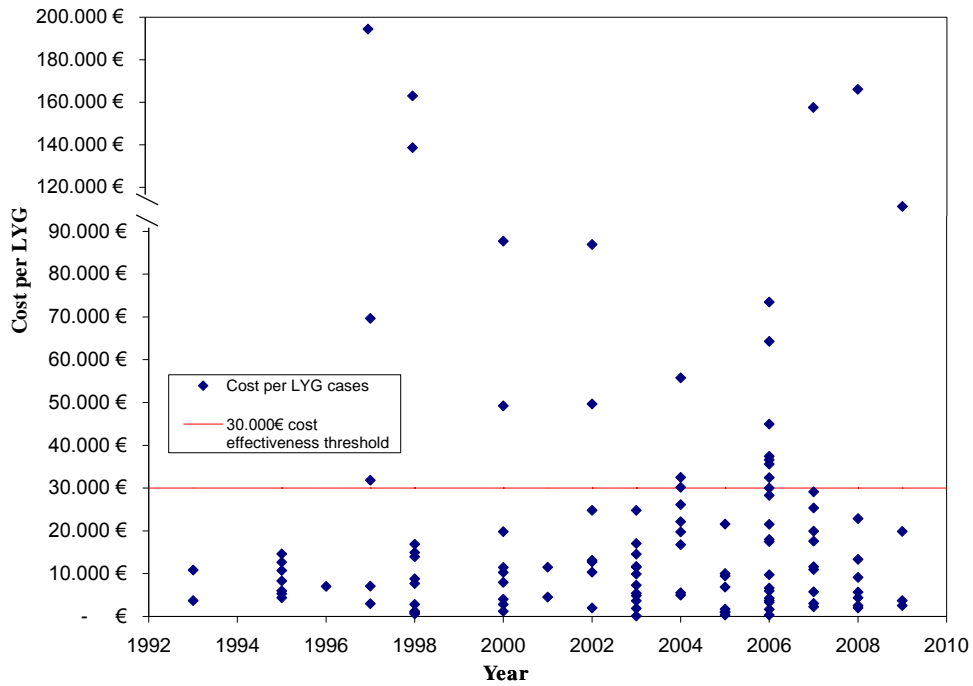
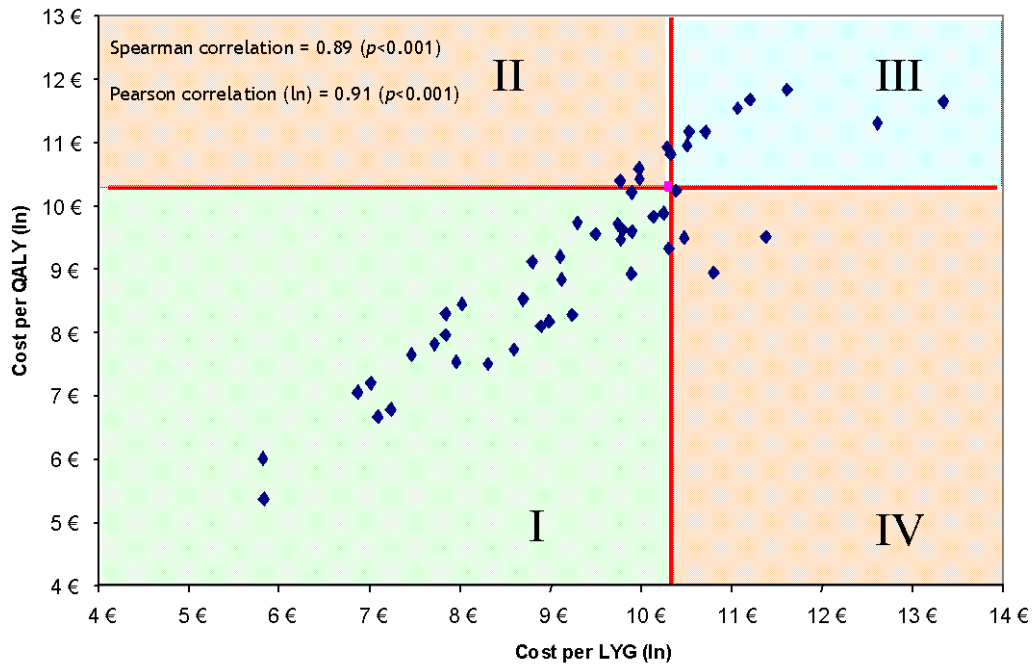


Figure 4. Study of cost per LYG and cost per QALY gained.



Cost effectiveness threshold (ln)= 10.31€ (equal to 30,000€/QALY gained)

The first and third quadrant show studies where cost per LYG and cost per QALY show the same (positive or negative) conclusion. Quadrant two shows studies where analysis by cost per QALY was not effective but cost per LYG was. Quadrant four shows studies where analysis by cost per LYG was not effective but cost per QALY was.

***Title Page**

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RESPONSE TO REVIEWERS COMMENTS

Ref.: Ms. No. EJHE-D-10-00140

The European Journal of Health Economics

Dear Mr. Pérez Alcántara,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

The reviewers' comments can be found at the end of this email or can be accessed by following the provided link.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript.

Your revision is due by 02-03-2011.

To submit a revision, go to <http://ejhe.edmgr.com/> and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely
Wolfgang Greiner
Managing Editor (Editorial Office)
The European Journal of Health Economics

Reviewers' comments:

Reviewer #1:

The manuscript EJHE-D-10-00140 is an interesting contribution to an important methodologic discussion, i.e. outcome measurement within the framework of health economic studies by means of life years gained (LYG) and cost per quality adjusted life year (QALY). The authors conducted a systematic review which aims at assessing the methodological quality of the increasing number of health economic evaluations in Spain and at investigating the relationship between the cost per LYG results and the cost per QALY. An additional analysis focuses on the question whether the recommended cost per LYG threshold published in Spain in 2002 has had an impact on afterwards published health economic evaluations.

In the discussion section (p. 6, line 37f) the authors state that "the number and quality of published Spanish health economic evaluations seems to improve as years go by". In order to support this statement, quality criteria are pointed out in the same paragraph. The authors argue that "in past reviews" certain standards or quality criteria were not sufficiently met. This finding should be described in greater detail in the results section. Is there a break-even point, for instance a specific publication date of a study or a review, which marks the onset of the quality gain in health economic assessments in Spain? Or is it a continuous process of quality improvement? This point should be described more precisely.

RESPONSE:

We now state in the section ICER analysis:

"However, a review by Sacristán et al. in 2002 found that most economic evaluations that recommended the adoption of a certain health intervention were based on ICE lower than 30,000 € per LYG [12]. This commonly-used threshold has been extended to cost per QALY and strengthened by the opinion of expert Spanish health economists [13]." Page 4 line 16

In the Results section we now state:

"Compared to previous systematic Spanish reviews [1,4], some methodological aspects seem to have improved. First, 82% of studies reviewed stated the perspective of the evaluation, compared to 28 and 43%, respectively, in previous reviews [1,4]. Second, the incremental cost and LYG differences are shown together with incremental ratios in 84% of studies. Third, 97% of studies conducted some form of sensitivity analysis, an essential requirement for any good economic evaluation, compared with only 30-68% [1,4] of past reviews. And fourth, although only 47% of studies stated the source of financing, this is greater than the 29% found in past reviews [4]." Page 7, line 21

And:

“As previously stated, a review published in 2002 found that most studies considered technologies with an incremental cost-effectiveness ratio below 30,000€ as efficient [12]. Our review showed that, since 2003, this unofficial threshold has been explicitly used as a reference by 66% of studies included.” Page 9, line 10

In the Discussion section we now state:

“Analysis of the methodological quality of the studies published since 2003, showed that 86% (30 of 35) were rated as (code++ or code +), showing the possible influence of previously published reviews in 2002 [1, 12] that may have led to greater methodological rigor. Moreover, it should be expected that the recent publication of Spanish recommendations on the economic evaluation of health technologies [11] will reinforce this trend in the future.” Page 11, line 6.

END RESPONSE

Another main critique is the following: At first sight, the significant correlation between cost per LYG and cost per QALY seems to be self-evident. Though, this correlation may vary across different types of diseases. The authors, being aware of this aspect, give examples for such as cancer and chronic illness (p. 7, line 46ff). Nevertheless, it is doubtful whether the statistical approach of this study is suitable for differentiating between the various illness conditions. The predominating impression after having read the paper is that the analyses equalize these differences rather than accentuating them.

RESPONSE:

We agree with the reviewer. We have added some points in the Discussion on this issue, and now conclude that:

“Therefore, larger studies where the primary objective is to analyse the relationship between ICE thresholds and types of diseases would be necessary. In the present study, only 9 out of 58 results, corresponding to 4 studies, showed this discrepancy, which is not sufficient to reach any conclusions.” Page 13, line 25.

END RESPONSE.

Reviewer #2:

Dear Editor/Dear Authors

The Manuscript Number EJHE-D-10-00140 "The use of cost per life year as cost Effectiveness Gained measure result in Spain. A recent publications review" is an interesting exercise in two complementary dimensions: first, it can provide guidance on the threshold of acceptability implicitly used in Spanish economic evaluation of health interventions, and second, it can provide answers to whether the Spanish authors have accepted the threshold discussed by Sacristán et al in 2002.

In my opinion, the authors commit two conceptual errors that influence the development of the manuscript.

First, Sacristán et al. (2002) did not suggest or advocate that the threshold of acceptability (incremental cost per additional life year gained) should be set at ? 30,000 / LYG. Sacristán et al., reviewed the Spanish papers on economic evaluation of health care interventions published from 1990 to 2000 and analyzed the recommendations of the authors of these works on what is supposed to be worth the incremental cost effectiveness ratio efficiently. Therefore, a part of the work of the authors of the manuscript EJHE-D-10-00140 had already been made by Sacristán et al. (2002).

Secondly, it is wrong to cite that "Later threshold cost per QALY extended to by the Spanish Health Economics Association [13]" The threshold of 30,000 ?/LYG has been never adopted or recognized by the Spanish Health Economics Association in the debate on the need for greater use of economic evaluation studies in healthcare decision making (<http://www.aes.es/Publicaciones/AESEE2.pdf>). The reference 13 is only the opinion of a member of the Spanish Health Economics Association issued individually, not on behalf of the Spanish Health Economics Association.

Therefore, my recommendation is that the manuscript EJHE-D-10-00140 was accepted for publication on condition that (a) the authors should carry out major changes in the manuscript and (b) the authors should focus their aim to respond if the threshold discussed in the work of Sacristán et al (2002) of ? 30,000 / LYG has been adopted as a reference in Spanish papers published in later years (from 2003 until now) or not.

RESPONSE:

We agree with the reviewer that no threshold was suggested either in the paper by Sacristan nor in any statement by the Spanish HEA and have revised the manuscript to emphasize this. We also include new material that addresses the question of whether the threshold suggested by Sacristán et al. have been adopted or has influenced Spanish papers published subsequently.

END RESPONSE.

More specifically:

1) The review of economic evaluation studies carried out between 1990 and 2000 was yet conducted by Sacristán et al. (2002). Authors are encouraged to focus their review in the period following the publication of the work of Sacristán et al., ie the period 2003-2009. The opposite is repeat work already done and published.

RESPONSE:

We agree with the reviewer that, to some extent, we have 'repeated' the review by Sacristán et al (2002), since we cover the period already analyzed in that paper. However, we believe that considering all economic evaluations (including those published before 2002) enabled us to better analyze the evolution of some aspects, such as the methodology quality of the studies or the potential influence of certain key publications like that by Sacristán et al. (2002). It also provides a larger sample size that may help in some of the analyses carried out.

END RESPONSE.

2) It would be interesting to include studies using the QALY as an outcome, since in the Spanish debate on the desirable value of the threshold, the figure of 30,000 euros has been used as a reference of a good value for a QALYs (eg reference 13).

RESPONSE:

A companion study using QALYs has already been carried out by Rodriguez-Barrios et al (2011, in press), the first author of the present study. Since C/LYG is also a commonly used C/E ratio, in this paper we wanted to focus on studies using C/LYG and introduce the comparison between this and C/QALY when both ratios were available (Rodriguez JM, Paz S, Lizan L, Gonzalez P. The use of Quality Adjusted Life Years (QALYs) in the economic evaluation of health technologies in Spain: a review of the 1990-2009 literature. Value in Health 2011 Volume 14 Issue 4.)

In the Discussion section we now state:

"One limitation of this study is the narrow focus on methodologies using cost per LYG as a result. However, we believe that a detailed examination of this particular topic was desirable, since a similar review focused on the results of studies using cost per QALY has been published elsewhere [5]." Page 11, line 13.

END RESPONSE.

3) The authors should be used as an element to consider whether in the studies reviewed made explicit references to the article of Sacristán et al. (indicating that the authors knew the threshold discussed) and if the authors explicitly compare their results with the threshold discussed by Sacristán et al. (2002). Finally, another item to discuss would be whether the authors' recommendations were based on a comparison of the results of their studies with the threshold of ?30,000 per LYG or ?30,000 per QALY. In most of the studies cited so it is. And this is a strong argument in favour of the endogenization of the threshold of 30,000 euros in the Spanish framework of the economic evaluation of health care technologies, contrary to what is suggested as a main conclusion of the manuscript.

RESPONSE:

In the Results section we now state:

“As previously stated, a review published in 2002 found that most studies considered technologies with an incremental cost-effectiveness ratio below 30,000€ as efficient [12]. Our review showed that, since 2003, this unofficial threshold has been explicitly used as a reference by 66% of studies included.” Page 9, line 10.

In the Discussion section we now state:

“Analysis of the methodological quality of the studies published since 2003, showed that 86% (30 of 35) were rated as (code++ or code +), showing the possible influence of previously published reviews in 2002 [1,12] that may have led to greater methodological rigor. Moreover, it should be expected that the recent publication of Spanish recommendations on the economic evaluation of health technologies [11] will reinforce this trend in the future.” Page 11, line 6

And

“Different thresholds have been stated in Spanish publications (ranging from 30,000€ to 50,000€/QALY) [12,21,22], but a recommendation of 30,000€/QALY gained is commonly considered as cost effective for most authors after the review by Sacristán et al. in 2002[12].” Page 12, line 10.

END RESPONSE.

4) It would be necessary to include control variables in the analysis or perform sensitivity analysis: Is it feasible to compare the results and findings of studies where the source of funding is private or where one or several authors works at private companies to the results and conclusions of studies where the source of funding is public or where the authors works at public organizations? Is it possible to compare the results and conclusions of the papers published in journals indexed in the Journal of Citation Report with those who are not?

RESPONSE:

We now state in the Results section:

“Analysis of the cost per LYG of all studies reviewed according to the source of funding showed that robust mean results were quite similar (11,539€ for privately-funded studies, 18,855€ for publicly-funded studies and 13,069€ for studies without the source of funding stated). However, this comparison is biased due to the small number (3) of publicly-funded studies.” Page 9, line 4.

We were not able to compare studies appearing in indexed and non-indexed journals because only 19 of the 124 cost per LYG results were from studies published in non-indexed journals.

END RESPONSE.

5) Similarly, the authors should discuss the potential existence of publication bias in the field of economic evaluation when the cost-effectiveness ratio found is very high. The manuscript would benefit from a thorough discussion on this topic.

RESPONSE:

We now state in the Discussion section:

“We found no clear influence of the commonly-used cost per LYG threshold of 30,000€ in studies published after the article by Sacristán et al (2002). However, an increase in the number of studies with cost per LYG results close to, but below, the 30,000€ threshold was found, which might indicate a certain temporary publication bias caused by the implicit acceptance of a threshold of efficiency, although more information would be needed to reach definitive conclusions.” Page 12, line 14.

END RESPONSE.

Minor comments:

Authors should review the manuscript and correct some typos.

RESPONSE:

The manuscript has been revised by an English native medical translator.

END RESPONSE.

I would like to stress that if the manuscript is reviewed according to these suggestions, the work will be of great interest not only for Spanish readers, as he delves into a very important issue for European health policy makers as the endogenization of explicit or implicit thresholds of acceptability in the field economic evaluation is.

I hope these comments are useful to the Editor and Authors

Yours sincerely