

# The Multinational Nature of Cost-Effectiveness Analyses Alongside Multinational Clinical Trials

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## ABSTRACT

**Objectives:** Applied and methodological evidence to the conduct of economic evaluations alongside multinational clinical trials have appeared in the literature over the last decade. Nevertheless, little is known about the number and identity of countries participating in these studies. A structured review was carried out to assess the reporting of the multinational nature of these studies.

**Methods:** A structured review was conducted by using online databases from January 1996 to December 2007. Articles were included if they reported cost-effectiveness analysis alongside a multinational randomized trial with individual patient-level data on resource use and outcome in more than one country. Key data extracted included country information, sample size, unit cost collection, methods to calculate costs and effects, and the reporting of incremental cost-effectiveness ratios.

**Results:** Sixty-five studies out of a total of 591 articles identified in the original search fulfilled the inclusion criteria and were included in the

review. Information about countries participating in the trial was not reported in 16 (26%) of the 65 studies. The overall sample size from all the randomized controlled trials identified was estimated to be 172,401 patients. Country-specific sample size was reported for 74,852 (43%) of the patients, but the country contribution was unknown for 97,549 (57%) of the participants.

**Conclusion:** The reporting of the multinational nature of these studies is currently inadequate. Therefore, future guidelines of transferability of economic evaluations across settings should emphasize the importance of reporting the number and identity of countries and their contribution to the overall sample size in cost-effectiveness analyses alongside multinational clinical trials.

**Keywords:** cost-effectiveness, economic evaluation, multinational randomized controlled trials, multinational studies, review.

## Introduction

Economic evaluation has become a valuable methodology to inform health-care resource allocation in many developed and developing countries [1,2]. As a result, there is an interest in evaluating whether economic evidence obtained in one location can meaningfully inform decision-makers in a different location [3,4] (in this article, the terms *location*, *jurisdiction*, and *setting* are used interchangeably). The extent to which such evidence can be transferred to another setting is often referred to as the generalizability of the study, recently defined by Sculpher et al. in an extensive report on this issue as follows:

generalisability of economic evaluation is the extent to which the results of a study based on a measurement in a particular patient population and/or a specific context hold true for another population and/or different context. [5]

Economic evaluations conducted alongside multinational clinical trials are a special case because they include by definition data from more than one patient population and one specific context. As a result, the analyst is potentially able to use information from that study to inform decision-makers in each of the countries that contributed patients. Such evaluations may also have wider generalizability to other settings because of greater heterogeneity represented in the patients participating. They are, therefore, a potential mechanism to improve generalizability of studies.

Conducting randomized controlled trials on a multinational basis is not a novel approach, and several authors have noted the

benefits associated with these study designs [6,7]. Conducting clinical trials across several countries may increase the recruitment rate and the sample size available for analyses. Consequently, the time needed to collect data, analyze, and present the results of the clinical trial can be significantly reduced. In addition, the clinical and research expertise and knowledge from experienced trial centers in a particular country can be transferred to centers with less experience in other countries. The pharmaceutical industry has found additional important advantages in running their studies across different countries [8–10]. For example, detailed information on unit costs, resource use, and effects can be collected across several jurisdictions, providing valuable data relevant to pricing, marketing, strategic planning, and reimbursement decisions in different markets.

Surveys of multinational economic evaluations have been published in recent years. Barbieri et al., for instance, identified 46 multinational economic evaluations of pharmaceuticals in Europe from 1998 to 2001 and suggested that variability of cost-effectiveness estimates across countries was influenced mainly by resource use differences and the real value of cost-effectiveness thresholds across jurisdictions [11]. Halliday and Darba explored how cost data were reported in 54 multinational economic evaluations for a period of 10 years up to 2002 and found wide variability in the quality of the reporting of these studies [12]. Both surveys included trial-based studies and economic models in their reviews.

Torti et al. identified 23 studies in a literature search from 1995 to 2004 of multinational economic evaluations alongside clinical trials in cardiology and extracted the categories of resources included, the costing strategies adopted, and extrapolation methods beyond the clinical trial period in these studies [13]. The authors concluded that more guidance is needed because design and analysis methods differed widely across studies.

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The review of generalizability by Sculpher et al. included a systematic review of economic evaluations undertaken alongside multicenter randomized controlled trials from 1994 to 2000 [5]. Multinational economic evaluations alongside clinical trials are by definition multicenter studies, and, hence, 21 studies of this type were retrieved in their review, which concentrated on identifying the type of cost analysis performed. They found that around 50% of the studies applied a single set of unit costs to resource use in all countries.

All these reviews have extracted important information to understand cost-effectiveness analysis alongside multinational clinical trials. Nevertheless, little is known about the multinational characteristics of such studies. For instance, information on the number of participating countries that contributed data and on their contribution to the overall sample size of the study have not yet been estimated. In addition, detailed data on the collection of unit costs and the type of analyses conducted across countries have been only partially reported [5,12,13]. Therefore, this article explores the multinational nature of multinational cost-effectiveness analyses using a structured review of published studies from 1996 to 2007.

## Methods

### The Structured Review

Articles were included if they reported cost-effectiveness analyses alongside a multinational randomized controlled trial with individual patient-level data on resource use and health outcomes in more than one country. For other relevant articles to be identified, articles were also included if analytical strategies either for resource use, health outcomes, or both that could assist in the performance of cost-effectiveness analysis alongside multinational clinical trials were explored. For the reporting of the review to be facilitated, the identified evidence was categorized in two groups: empirical or applied evidence, and methodological studies.

These inclusion criteria ensured retrieval of, for example, the main cost-effectiveness results from a trial and a second publication using the same trial data to explore a methodological question such as different methods of analyzing cost-effectiveness analysis alongside multinational clinical trials. In this case, the former article would be categorized as empirical, whereas the latter would be categorized as methodological. Recent articles have provided good overviews on the methodology surrounding the analysis and presentation of results from multinational cost-effectiveness analysis [14,15]. Consequently, this article concentrates in reviewing and extracting those publications categorized as empirical or applied only.

Cost-effectiveness analyses alongside nonrandomized multinational clinical trials, economic models, published abstracts of conference proceedings, research protocols, discrete choice experiments, and willingness to pay studies were not included in the review.

The core search strategy was performed in MEDLINE, EMBASE and the National Health Service economic evaluation database. Cross-reference searching of eligible articles was also carried out.

Different spellings and combinations of the following terms were used in the search strategy: multinational, clinical, trial, randomized, multicountry, cost, cost-effectiveness, cost-utility, cost-benefit. The use of terms that potentially could retrieve a large list of unsuccessful results, such as "country/ies" or "multicenter/center" was avoided (some authors use the term "multicenter/center" to refer to multinational studies, and omitting this term in the search strategy could have left potential

evidence unidentified. Nevertheless, it was expected that cross-references would help to identify these articles and minimize any potential bias).

Articles published from January 1996 to December 2007 were included in this review.

The title and abstract of all articles identified were reviewed, and if they fulfilled the inclusion criteria, a complete printed document was electronically downloaded or ordered. For ambiguous results, a full document was also retrieved and examined.

A keyword *pro forma* was developed for the extraction of data. The main information extracted included

1. the overall sample size of the trial;
2. the number of participating countries and their corresponding contribution to the sample size;
3. the categories of resource use collected;
4. the sources for unit costs, the country of origin, and adjustments for missing unit cost information;
5. the sources and methods to calculate costs;
6. the currency adjustment adopted;
7. the sources and methods used in the effectiveness analysis; and
8. the reporting of the incremental cost-effectiveness results (ICERs).

The World Bank income classification that divides countries according to 2007 gross national income (GNI) per capita was used in the RESULTS section: low income, \$935 or less; middle income, \$936 to \$11,455; and high income, \$11,456 or more. For trends across the study period of the review to be estimated, estimates were also calculated and presented from the periods from 1996 to 2000 and from 2001 to 2007.

All analyses were carried out in Excel 2007 and STATA 10 [16]. Descriptive statistics and standard statistical tests were used to report the results of this review.

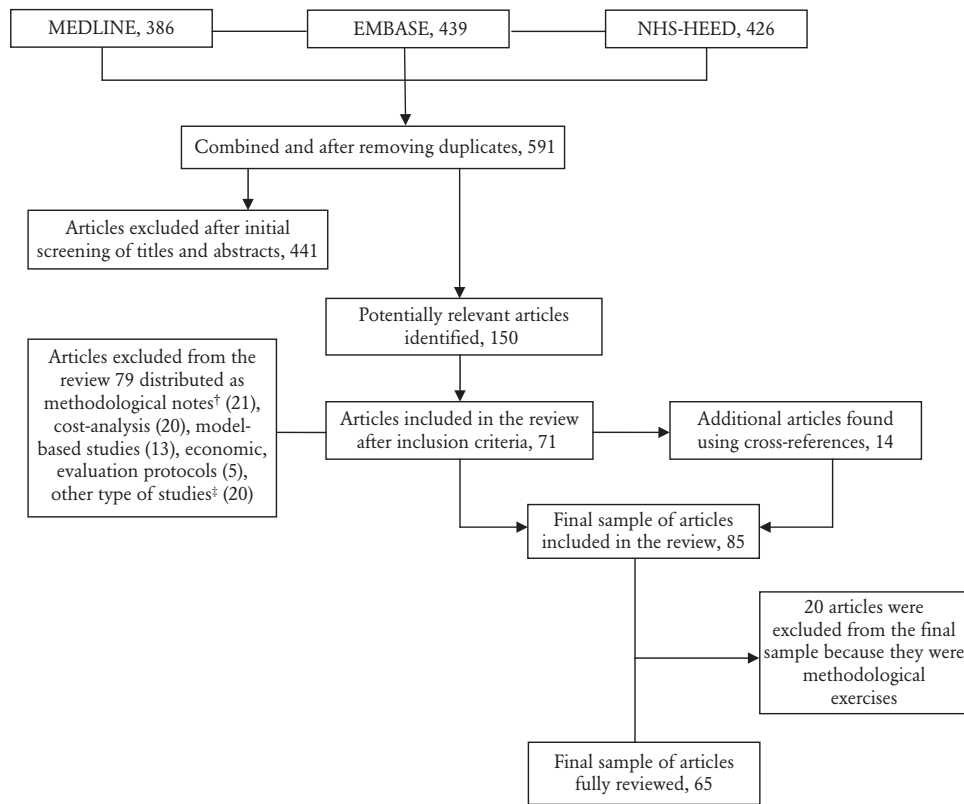
### Classification of the Analytical Approach of Studies

The terminology proposed by Reed et al. to describe the analytical approach used in multinational economic evaluations alongside trials is adopted in this review to categorize the studies [17]. Studies are classified first depending on whether patients in a single country (or a subset of countries) or patients in all countries contributed to the sample size for the effectiveness and resource use data used in the analysis. A fully pooled analysis is based on effectiveness and resource use data from patients in all countries. A partially split analysis is based on estimates of effectiveness data from all countries, but resource use data are based on a single country (or a subset of countries). In a fully split analysis, estimates of effectiveness and resource use are based on the same group of patients in a single country (or a subset of countries). Studies are then further classified, depending on the costing method performed. If unit cost estimates from each particular country are applied to the resources used in those countries, it is described as a multicountry costing. In a one-country costing, a unit cost estimate from one country is applied to resource use in all countries, a subgroup of countries, or a single country.

## Results

### Descriptive Information of the Overall Review

A schematic diagram of the overall identification and review process is presented in Figure 1. A total of 591 articles were identified from the original search strategy. From those, 441 articles were excluded because they clearly did not fulfill the inclusion criteria. The majority of these articles were economic

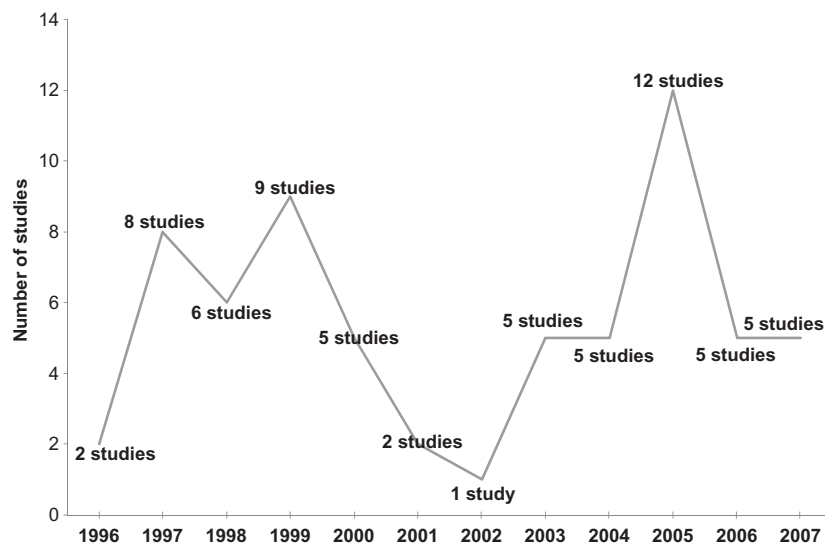


**Figure 1** Schematic diagram of overall identification and review process. <sup>†</sup>Research consensus, international comparisons, and general review. <sup>‡</sup>Willingness to pay analysis, travel costs evaluations, noneconomic evaluation studies, and nonrelated research. NHS-HEED, economic evaluation database.

evaluation models, cost-analyses using data from randomized and nonrandomized designs, and nonrelated research. Full printed copies were obtained from 150 potentially relevant articles. After careful evaluation, 79 articles were excluded from the review, leaving 71 articles fulfilling the inclusion criteria. Cross-reference checks from the identified studies yielded another 14 relevant articles. The final sample of this review

comprises 65 studies after methodological exercises were excluded. A list of the references of this final sample is presented and can be found at: [http://www.ispor.org/Publications/value/ViHsupplementary/ViH13i1\\_Rivero-Arias.asp](http://www.ispor.org/Publications/value/ViHsupplementary/ViH13i1_Rivero-Arias.asp).

The frequency of studies published annually since 1996 is presented in Figure 2. The chart shows no clear trend in the frequency of multinational economic evaluation publications.



**Figure 2** Frequency of multinational economic evaluations published from 1996 to 2007.

### The Multinational Nature of the Studies

Detailed information on the number of participating countries and their contribution to the overall sample size was reported in 20 (31%) of the 65 studies. A total of 29 (45%) of the 65 publications provided limited information about their international dimension, for example, articles that mentioned the number of participating countries but provided no information on which countries were included or the contributing sample size from each country. Finally, 16 (25%) of the 65 studies did not report any information on the multinational nature of the study.

A detailed examination of countries contributing data and of the number of studies to which data were contributed is presented in Table 1. The overall sample size from all the randomized controlled trials identified was estimated to be 172,401 patients. Country-specific sample size was reported for 74,852 (43%) of the patients, but the country contribution was unknown for 97,549 (57%) of the participants. A total of 53,852 (72%) of the patients in studies reporting country-specific sample size came from high-income countries, and 11,070 (15%) from middle-income countries. The majority of middle-income countries participating in these studies did so during 2004 and 2005. Centers from the United Kingdom participated in 23 of the studies, making the UK the country with the most frequent involvement in research of this type. Nevertheless, the United States recruited the largest number of patients across all countries identified in the review.

Table 2 provides estimates on the multinational nature of the studies included in the review. A total of 31 (48%) of the 65 studies were conducted entirely in high-income countries and contributed 63,693 (37%) patients to the overall reported sample size across all studies. The mean (range) number of countries per study was estimated to be 7 (2–33) across all studies and 5.5 (2–15) across studies in high-income countries, a nonsignificant difference ( $P = 0.1794$ ). The mean (range) sample size per study was estimated to be 2655 (44–14,703) across all studies and 2055 (44–10,305) across studies in high-income countries, a nonsignificant difference ( $P = 0.4039$ ).

Table 2 also shows the mean (range) proportion of patients from the largest contributing country by study period. Nonsignificant differences were found between groups and across time period (1996–2000:  $P = 0.900$ ; 2001–2007:  $P = 0.5726$ ). The largest contributing country recruited, on average, around 38% of all the patients participating in the study.

Table 3 shows the unit cost collection approach used in the studies. A total of 39 (62%) of the 63 studies collected unit costs data from one country and had an associated mean (range) of 5.6 (2–16) countries per study. Studies collecting unit cost information from two to four countries had a mean (range) of 5.4 (2–12) countries per study. Thirteen (21%) studies collected unit cost data from more than four countries, and 11.9 countries participated in these studies on average. An analysis of variance confirmed a significant difference in the mean number of countries per study among groups ( $F = 6.08$ ,  $P < 0.01$ ). No differences in the collection of unit costs were found across time.

Table 4 reports the type of unit costs data collected within each country. The majority of studies collected national average unit costs or used mixed sources to perform the cost analysis. It seems that there has been a move from using mixed sources toward national average unit costs after 2000, but no statistical difference between periods was detected to validate this result ( $\chi^2 = 8.59$ ,  $P = 0.072$ ).

### The Collection of Effectiveness Data

A total of 58 (89%) of the 65 studies used trial-wide health outcome data to conduct their effectiveness analysis, indicating

**Table 1** Description of countries contributing data and number of studies to which data were contributed by using the World Bank classification category

Country	Number of patients reported	Percentage (%) contribution from overall sample size	Number of studies
<b>High-income countries</b>			
US	19,926	11.56	18
Canada	5,042	2.92	14
Sweden	5,029	2.92	16
UK	3,266	1.89	23
Italy	2,639	1.53	11
Norway	2,518	1.46	11
The Netherlands	2,284	1.32	11
Denmark	2,278	1.32	14
Finland	2,069	1.20	11
Germany	1,989	1.15	17
France	1,281	0.74	21
Greece	966	0.56	3
Spain	925	0.54	18
Australia	744	0.43	9
Hungary	584	0.34	4
Belgium	466	0.27	11
Czech Republic	379	0.22	3
Iceland	314	0.18	3
Austria	218	0.13	6
Luxembourg	185	0.11	1
Slovak Republic	184	0.11	1
Switzerland	174	0.10	5
New Zealand	144	0.08	2
Israel	85	0.05	3
Portugal	72	0.04	3
Singapore	46	0.03	1
Ireland	38	0.02	2
United Arab Emirates	7	0.00	1
<b>Total high income</b>	<b>53,852</b>	<b>31.22</b>	
<b>Middle-income countries</b>			
Russia	3,146	1.82	3
South Africa	2,980	1.73	7
Argentina	2,291	1.33	5
India	718	0.42	1
Colombia	474	0.27	1
Brazil	401	0.23	4
Poland	348	0.20	2
Cuba	254	0.15	1
Albania	108	0.06	1
Egypt, Arab Rep.	108	0.06	1
Mexico	67	0.04	3
Turkey	46	0.03	1
Venezuela, RB	33	0.02	1
Malaysia	32	0.02	1
Jordan	28	0.02	1
Thailand	20	0.01	1
Sri Lanka	8	0.00	1
Chile	4	0.00	2
Peru	2	0.00	1
Uruguay	2	0.00	1
<b>Total middle income</b>	<b>11,070</b>	<b>6.41</b>	
<b>Low-income countries</b>			
Zimbabwe	611	0.35	1
Uganda	584	0.34	1
Nigeria	466	0.27	1
Pakistan	297	0.17	1
Bangladesh	196	0.11	1
Malawi	109	0.06	1
Yemen Rep.	109	0.06	1
Ghana	106	0.06	1
Sierra Leone	34	0.02	1
<b>Total low income</b>	<b>2,512</b>	<b>1.44</b>	
Other(s)*	7,418	4.30	
<b>Total country sample size reported</b>	<b>74,852</b>	<b>43.42</b>	
Unknown country contribution	97,549	56.58	
<b>Total sample size from all randomized controlled trials</b>	<b>172,401</b>		

\*Some articles reported sample size by regions but did not clarify the participating countries (e.g., Europe, South America, Western Europe, North America).

**Table 2** Descriptive statistics of the multinational nature of the studies included in this review

	n	All studies	n	Studies conducted entirely in high-income countries
Total number of studies		65		31
Total number of participating countries		57		28
Total sample size across studies		172,401		63,693
Mean (range) number of countries per study	48	7 (2–33)	30	5.5 (2–15)
Mean (range) sample size per study	65	2,655 (44–14,703)	31	2,055 (44–10,305)
Mean (range) sample size per country	199	376 (1–3,964)	57	448 (1–3,522)
Mean (range) proportion of patients from the largest contributing country*				
Overall				
1996–2000	8	0.37 (0.20–0.60)	6	0.36 (0.20–0.60)
2001–2007	12	0.37 (0.11–0.75)	5	0.43 (0.11–0.75)

\*These parameters could only be calculated by using studies that reported detailed information on the countries participating and contributing sample size.

the dominance of fully pooled and partially split methods in this type of study (Table 5). Although no differences were found in the analysis and reporting of effectiveness data across periods, the number of studies using health-related quality of life data seems to have increased over the years. Quality adjusted life-years (QALYs) were used as the main outcome measure in nine studies, with the EuroQol five-dimension generic instrument (EQ-5D) UK tariff, the EQ-5D thermometer, and mapping algorithms being the main approaches used to calculate utility values.

### The Reporting of Cost-Effectiveness Analysis

Fully pooled, one-country costing with 66% (43 of the 65 articles) and fully pooled, multicountry costing with 15% (10 of the 65 publications) were the preferred methodological approaches adopted to analyze and report the results from these studies (Table 6). Fully and partially split were less common, being used in studies where the proportion of patients from the largest contributing country was greater than 45% on average.

Although no significance differences between periods were detected ( $\chi^2 = 7.31$ ,  $P = 0.121$ ), a description of the methodological approaches by year of publication is presented in Figure 3.

Table 7 shows that country-specific ICERs were reported in 10 (15%) of the 65 studies and that one estimate of ICER for all countries was reported in 25 (38%) of the 65 studies. ICERs were not reported in 24 (37%) of the 65 articles, but this was particularly a characteristic in studies published before the year 2000 [16 (53%) of the 30 studies] with the reporting improving significantly after then, with only 8 (23%) of the 35 studies not combining costs and effects. A similar pattern was observed in the studies when handling uncertainty for the ICERs. Table 8 suggests a significant improvement when reporting measures of uncertainty for ICERs after the year 2000.

Detailed results of the cost-effectiveness analyses performed in multicountry studies and studies reporting country-specific ICERs are presented and can be found at: [http://www.ispor.org/Publications/value/ViHsupplementary/ViH13i1\\_Rivero-Arias.asp](http://www.ispor.org/Publications/value/ViHsupplementary/ViH13i1_Rivero-Arias.asp).

### Funding of Studies

A total of 53 (82%) of the 65 studies identified in this review were funded by the pharmaceutical industry; 5 (7%) of the 65 were funded by nonindustry organizations, and the remainder 7 (11%) of the 65 did not specified the funding received. The studies funded by the pharmaceutical industry comprise 135,521 (79%) of the overall sample size from all the randomized controlled trials and were conducted exclusively in high-income countries in 24 (62%) of the 39 studies.

### Discussion

Using a structured review, this review identified 65 cost-effectiveness analyses alongside multinational clinical trials from 1996 to 2007 and extracted relevant information on the multinational nature of these studies. Around 57% of the overall sample failed to describe the contribution of the countries participating in the trial, indicating poor reporting of the multina-

**Table 3** Unit costs information used in the costing analysis in the studies included in the review

Collection of unit cost information	Number (%) of studies*	Mean (range) number of countries in the study
Overall		
Unit cost from one country only	39 (62)	5.6 (2–16) <sup>†</sup>
Unit cost from 2–4 countries	11 (17)	5.4 (2–12) <sup>†</sup>
Unit cost from 5+ countries	13 (21)	11.9 (5–33) <sup>‡</sup>
1996–2000		
Unit cost from one country only	19 (66)	5.1 (2–15)
Unit cost from 2–4 countries	5 (17)	3.6 (2–6)
Unit cost from 5+ countries	5 (17)	7.4 (5–15)
2001–2007		
Unit cost from one country only	20 (59)	5.9 (2–16) <sup>‡</sup>
Unit cost from 2–4 countries	6 (18)	6.8 (4–12) <sup>‡</sup>
Unit cost from 5+ countries	8 (24)	14.8 (6–33) <sup>‡</sup>

\*Two countries did not provide detailed data in the collection of unit costs across countries.

<sup>†</sup>F = 6.08,  $P < 0.01$ .

<sup>‡</sup>F = 5.15,  $P = 0.01$ .

**Table 4** Unit cost collection approach used in the studies included in the review

	Single center (%)	Multiple center unit costs (%)	National average unit costs (%)	Mixed sources (%)	Not clear (%)	Number of studies
Overall	3 (5)	3 (5)	35 (54)	21 (32)	3 (5)	65
1996–2000	2 (7)	2 (7)	11 (37)	12 (40)	3 (10)	30
2001–2007	1 (3)	1 (3)	24 (69)	9 (26)	0 (0)	35

**Table 5** Health outcome data collected and type of effectiveness analysis conducted in the studies

Summary of effectiveness analysis	Overall (%)	1996–2000 (%)	2001–2007 (%)
Handling of the effectiveness data			
Trial-wide effectiveness data used	58 (89)	26 (87)	32 (91)
Subsample of cases used	7 (11)	4 (13)	3 (9)
Health outcomes used in the analysis			
Disease-specific	28 (43)	16 (53)	12 (34)
Life-years	23 (35)	11 (37)	12 (34)
HRQoL			
EQ-5D	9 (14)	1 (3)	8 (23)
SF-36	2 (3)	1 (3)	1 (3)
Other	3 (5)	1 (3)	2 (6)
Utility calculation in studies presenting quality-adjusted life-year (QALYs)			
EQ-5D UK tariff	4 (44)	—	4 (57)
EQ-5D thermometer	2 (22)	1 (50)	1 (14)
Utility mapping	3 (33)	1 (50)	2 (29)

EQ-5D, Euroqol five-dimension generic instrument; HRQoL, health-related quality of life; QALYs, quality-adjusted life-years; SF-36, short-form 36 items generic instrument.

tional dimension. In addition, approximately 20% of the articles did not recognize the multinational nature of the study in any section of the article.

In most studies, one country contributed a large proportion of the overall sample size. This was clearly influential when deciding on the method to analyze cost-effectiveness data. Studies where the largest country contributed less than 36% of the total sample size preferred a fully pooled costs and effects approach to

**Table 7** Presentation of country-specific ICER results in the applied studies

Classification	Overall (%)	1996–2000* (%)	2001–2007* (%)
One estimate of ICER was reported for all countries	25 (38)	8 (27)	17 (49)
Not reported	24 (37)	16 (53)	8 (23)
Country-specific ICERs were reported for each country <sup>†</sup>	10 (15)	2 (7)	8 (23)
One estimate of ICER for a particular country	6 (9)	4 (13)	2 (6)
Total	65	30	35

\*Statistical significant difference between periods  $\chi^2 = 9.85$ ,  $P = 0.020$ .

<sup>†</sup>The study by Simon et al. [18] divides group of patients by GNI and does not report ICERs by country but GNI regions.

GNI, gross national income; ICER, incremental cost-effectiveness ratio.

conduct their analyses. Nevertheless, studies where one country contributed 45% or more of the total generally split the data instead of pool them across all countries.

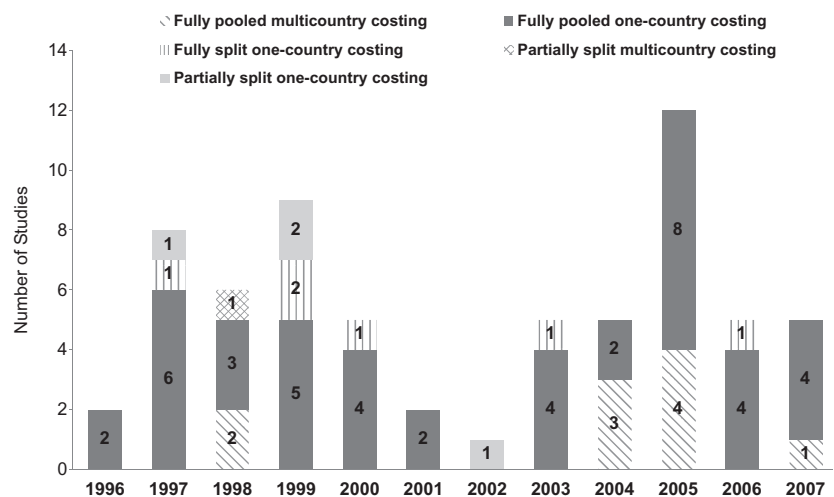
The selection of countries in the studies was conducted ad hoc rather than at the design stage. The implications of this selection are still under evaluation, but a number of methods have already been suggested to deal with this issue. Current statistical methods to analyze costs and outcomes data across settings suggest the use of multilevel models to estimate cost-effectiveness [15]. Multilevel models require a large number of units in the level indicating the cluster, that is, number of countries, to ensure variability between levels. On average, seven countries per study

**Table 6** Ways in which cost-effectiveness data were analyzed in the studies by using Reed et al. [17] classification

Classification	Overall Freq (%)	1996–2000 Freq (%)	2001–2007 Freq (%)	Detailed information studies (n)	Mean (range) proportion of patients from the largest contributing country*
Fully pooled, one-country costing	43 (66)	19 (63)	24 (69)	9	0.32 (0.11–0.44)
Fully pooled, multicountry costing	10 (15)	2 (7)	8 (23)	6	0.36 (0.20–0.54)
Fully split, one-country costing	6 (9)	4 (13)	2 (6)	3	0.46 (0.24–0.75)
Partially split, one-country costing	5 (8)	4 (13)	1 (3)	2	0.49 (0.40–0.60)
Partially split, multicountry costing <sup>†</sup>	1 (2)	1 (3)	0	—	
Total	65	30	35		

\*These parameters could only be calculated by using studies that reported detailed information on the countries participating and contributing sample size.

<sup>†</sup>This classification is possible if health outcomes have been analyzed by using data from all countries, but costs have been analyzed by using a subset of countries.

**Figure 3** Description of methodological approaches used in the studies by year of publication.



**Table 8** Handling uncertainty for the incremental cost-effectiveness ratio (ICER) estimates in the applied studies

Classification	Overall (%)	1996–2000* (%)	2001–2007* (%)
No uncertainty presented	37 (57)	23 (77)	14 (40)
Deterministic sensitivity analysis	2 (3)	1 (3)	1 (3)
Uncertainty handled through statistical methods	26 (40)	6 (20)	20 (57)
Total	65	30	35

\*Statistical significant difference between periods  $\chi^2 = 9.40$ ,  $P = 0.009$ .

contributed to the data collection in the trials. Therefore, it is likely that the use of this method in the majority of studies identified in this review would have been very limited [15].

A total of 31 of the 65 studies identified were conducted exclusively in high-income countries, and the remainder also recruited heavily from high-income countries. A weak trend of countries from middle-income countries participating in these studies was identified during the years 2004 and 2005. Nevertheless, this trend disappears after that period. All the low-income countries identified in this review participated in just one of the studies [18]: the study by Simon et al. comparing the use of magnesium sulfate for the treatment of pre-eclampsia. This low participation rate from low-income countries perhaps explains why disability-adjusted life-years were not used as the primary outcome measure in any of the studies.

This review attempted to identify whether the reporting of the multinational nature of these studies had improved over the years. Although some trends were observed between time periods, few significant differences were detected probably because of the small sample size of 65 studies in the review. Nevertheless, the significant improvement in the reporting of ICERs and handling of uncertainty after 2000 suggests that guidelines on the conduct of economic evaluation of health-care technologies have had some effect.

Several discussions on generalizability and transferability of economic evaluations across geographic locations have recently been published [5,15,19–21]. The ISPOR Good Research Practices Task Force Report, for example, reviewed what current national guidelines in economic evaluation state about transferability [15]. The report suggested that most guidelines did mention transferability and the potential of using information from a different jurisdiction to inform their own setting, but recommendations on how to use external information varied across national guidelines. The Task Force Report emphasized the use of multilocation clinical trial data to adjust cost-effectiveness information for a particular setting. It was suggested that descriptive statistics and tests for heterogeneity should be explored first to identify any potential differences across jurisdictions. Then, more sophisticated statistical modeling should be implemented to adjust cost-effectiveness estimates in a particular location. The use of these methods should be guided by the following criteria: “1) number of jurisdictions (e.g., countries, centers); 2) exchangeability or nonexchangeability of data; and 3) the availability of covariates (e.g., center and country level)” [15]. Nevertheless, the present review suggests that quite basic information such as the number and identity of countries participating is currently reported inadequately. Therefore, decision-makers will find it difficult to decide whether a particular study is of interest to their own setting.

Individual patient-level data from multinational clinical trials are likely to inform parameters in model-based studies, which aim to inform cost-effectiveness in a particular country. This type

of study was not included in the current review, and, currently, little is known about the quality of these studies. Future reviews should extract relevant information that helps fill the current gap in the literature on this issue.

Only one assessor evaluated the evidence included in the final sample of this review, and, although the search was performed in a transparent and structured manner, the final sample included in the review cannot be considered exhaustive. Nevertheless, the large number of references extracted compared with other reviews suggests that, if any relevant evidence was left unidentified, it is unlikely to cause bias in the results.

The results from this review suggest that future guidelines on transferability of economic evaluations across settings should emphasize the importance of reporting the number and identity of countries and their contribution to the overall sample size in cost-effectiveness analyses alongside multinational clinical trials. Both analysts and decision-makers will benefit from this improvement. From the analyst's side, reporting participating countries and contributing sample size will improve the overall quality of the study. Decision-makers will also greatly benefit from this improvement because they will be better informed on the relevance of the study to their particular setting.

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