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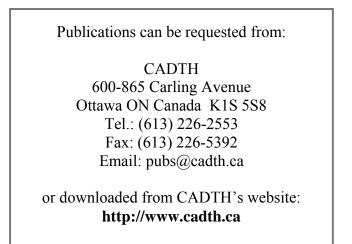## English-Language Restriction When Conducting Systematic Review-based Meta-analyses: Systematic Review of Published Studies

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Supporting Informed Decisions

Canadian Agency for Drugs and Technologies in Health

English-Language Restriction When Conducting Systematic Review-based Meta-analyses: Systematic Review of Published Studies

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The lead author, Andra Morrison, developed the initial protocol, led the research, and coordinated the project. She participated in the selection of included studies, data extraction, and design and execution of the literature search strategies; contributed to the environmental scan; wrote the draft; revised the report; and prepared the report for publication.

Kristen Moulton played a role in the selection of the included studies, assisted in data extraction, participated in the scanning of Cochrane and CADTH publications for inclusion of articles in languages other than English, contributed to the initial draft of the review, and provided comments and feedback regarding drafts.

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Julie Polisena was involved in the study quality assessment and the tabulation and analysis of data and assisted in the writing of the report.

Shaila Mensinkai provided feedback on the development of the search strategy, was involved in facilitating the environmental scan, and participated in the selection of included studies.

Monika Mierzwinski-Urban provided comments and feedback on the initial protocol, peer-reviewed search strategies, and participated in the selection of included studies.

Michelle Fiander provided comments and feedback on the initial protocol and assisted in the selection of included studies.

Tammy Clifford assisted with the development of the protocol, participated in the selection of included studies, participated in discussions on included and excluded studies, reviewed drafts, and provided comments.

Brian Hutton participated in data extraction and revision of intermediate drafts and contributed to the preparation of the final draft.

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Conflicts of Interest

Margaret Sampson was a member of the research team that conducted some of the studies included in this review. She did not have a role in performing any of the included research.

The authors have no conflicts of interest to declare.

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1   INTRODUCTION

1.1 Background

The English language is generally perceived to be the universal language of science.[1,2] The top 10 international medical journals in 11 medical specialties (measured by impact factor) are English-language publications.[3] The exclusive reliance, however, on data that are published in English and that are used as the basis of systematic reviews of health care interventions may not result in an accurate representation of existing evidence. Excluding languages other than English (LOE) may lead to erroneous conclusions, because a language bias is introduced.

Systematic reviews provide one of the highest levels of clinical evidence.[4] Chalmers and Altman defined a systematic review as "a review that has been prepared using a systematic approach to minimising biases and random errors which is documented in a materials and methods section. A systematic review may, or may not, include a meta-analysis: a statistical analysis of the results from independent studies, which generally aims to produce a single estimate of a treatment effect."[5] A systematic review is an evidence-based critical assessment and synthesis of the results of trials or studies. This information can be used to shape medical decision making, to inform policy makers, to keep health care practitioners up to date, and to highlight areas where more research is needed.[6,7]

The validity of a systematic review is partially based on a comprehensive literature search. *The Cochrane Handbook for Systematic Reviews of Interventions*, which details the process of preparing Cochrane systematic reviews, defines a comprehensive search strategy as being replicable and thorough and as including a search of various sources.[8] A comprehensive search strategy involves the development and implementation of a strategy that will lead to the identification of relevant published and unpublished studies from indexed biomedical databases and grey literature sources. It is recommended that a comprehensive search strategy include the use of two or more databases (with a consideration of the unique contributions of each database); the hand-searching of the bibliographies of selected articles, conference proceedings, and abstracts; and personal communications with researchers.[9,10] These steps are advocated because they help to overcome selection biases.[7]

The introduction of bias can influence the results of systematic reviews and lead to inaccurate pooled estimates of the effect measures. Many factors can alter the estimate of an intervention's effectiveness. In addition to language restriction,[11] other systematic biases have been attributed to publication status,[12] sources of funding,[13] outcome reporting,[12] the databases that were searched,[14] study quality,[12] grey literature,[12] and reviewers.[15] This systematic review focuses on the impact of language restriction.

Language bias typically refers to a systematic bias due to the selection of research findings in a particular language.[7] There is concern that papers reporting positive results are more likely to be published in English-language journals and that papers reporting negative results are more likely to be published in non-English-language journals. This is known as "Tower of Babel" bias[16] or "English-language" bias.[1] If this bias is introduced, there may be an over- or underestimation of

an intervention's effectiveness, leading to inappropriate treatment decisions and suboptimal population health.[16]

The Cochrane Handbook suggests that, whenever possible, language restrictions should be avoided.[8] The UK National Health Service Centre for Reviews and Dissemination advises that reports be included irrespective of language and that the impact of papers that are written in LOE on the estimation of effects be examined in a sensitivity analysis.[17]

2 THE ISSUE

The barriers to the inclusion of papers that are written in LOE in systematic reviews include the time and the cost of acquiring and translating articles. It is uncertain whether the time that is needed for the retrieval and translation of citations that are written in LOE is justified when it is weighed against the potential for further minimization of bias. The process can prolong the duration and increase the cost of a systematic review.

3 OBJECTIVES

The primary research objective was to review the published and unpublished evidence on the impact of language restrictions on systematic review-based meta-analyses (SR/MA). Another objective was to review Canadian and international health technology assessment (HTA) agencies' language inclusion practices when conducting these studies. To meet these objectives, this report addresses three research questions.
- What is the impact of including or excluding data from primary research published in LOE on summary treatment effect estimates when conducting SR/MA?
- What are the other effects associated with the exclusion of primary research published in LOE?
- What are the current practices and policies of international HTA agencies, and how do they compare with the Canadian Agency for Drugs and Technologies in Health's (CADTH's) language policies?

4 METHODS

A protocol for this review was written a priori and adhered to with no deviations.

4.1 Literature Search Strategy

A comprehensive search strategy was developed and implemented by an information specialist with input from the project team. The search strategy was reviewed by another CADTH information specialist.

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The following bibliographic databases were searched through the Ovid interface: MEDLINE (1966 to September week 3, 2007), MEDLINE In-Process & Other Non-Indexed Citations (September 13, 2007), EMBASE (1988 to week 36, 2007), BIOSIS Previews (1989 to week 39, 2007, CINAHL (1982 to week 1, September 2007), and Cochrane (3rd quarter, 2007). The Cochrane Methodology Register and the Cochrane Bias Methods Group were searched through the Wiley version of the Cochrane Library.

A search strategy with controlled vocabulary and key words was developed to identify relevant literature on the evidence and methodological issues pertaining to language bias in the reporting of trials (Appendix 1).

The search was restricted to articles that were published from 1990 onwards and that assessed the impact of including or excluding randomized controlled trials (RCTs) that are reported in LOE in SR/MA of conventional medical interventions.

Grey literature (literature that is not commercially published) was identified by searching the websites of HTA and related agencies, professional associations, and specialized databases. Google and Yahoo! search engines were used to search for additional information. These searches were supplemented by hand searches of the bibliographies and abstracts of key papers and conference proceedings and of reference lists and through contacts with appropriate experts and agencies.

OVID AutoAlerts were set up to provide monthly updates of new literature from 18 September 2007 to 13 March 2008. The search was not limited by language of publication, methodological design, or publication status.

4.2 Selection Criteria

Studies were eligible for inclusion in this review if they sought to measure the effect of excluding RCTs that are reported in LOE from SR/MA for one or more meta-analyzed outcomes (summary treatment effect). Only studies that assessed bias from SR/MA of conventional medicine interventions were included. The US National Cancer Institute's definition of conventional medicine was adopted for this study, "[A] system in which medical doctors and other healthcare professionals (such as nurses, pharmacists, and therapists) treat symptoms and diseases using drugs, radiation or surgery."[18] Reports that focused exclusively on complementary and alternative medicine (CAM) were excluded, because CADTH does not routinely assess CAM interventions.

4.3 Selection Method

Because of the anticipated retrieval of a large volume of records, two screening levels and one relevance assessment level were used. The first level of screening was based on the title only. The abstracts (if available) of citations that were judged by two independent reviewers (AM, and KM or MC) as "include" or "unclear" at the first level were retrieved. At the second level, two independent reviewers (AM and KM) judged the title and abstract of citations that were not excluded at level 1. Reports that were designated as "include" or "unclear" at the second level were retrieved in full text.

Two reviewers (AM and KM) independently assessed each paper for final inclusion. Reviewers were not blinded to the identification of authors or affiliated institutions, because there is no evidence that such practices influence results.[19] To be included, a paper had to satisfy all the predetermined eligibility criteria. Any disagreement about the inclusion of a study was resolved by discussion. When agreement could not be achieved, a third reviewer had to cast a deciding vote.

4.4 Data Extraction Strategy

After selection of the relevant studies, two reviewers independently extracted and tabulated outcome data using a standard form. Outcome data included country of origin, research objectives, study design, databases, years searched, number of included studies, and number of reviewers (Appendix 2). Where necessary, text descriptions were used to highlight information that was not captured in the table. Any discrepancies between reviewers were discussed until a consensus was reached. The reviewers contacted the authors of included studies for additional information as required.

4.5 Methodological Quality Assessment

We modified a checklist that was originally validated for human analytic studies[44] to assess the quality of studies that were identified in our systematic review. The checklist questions relate to domains of reporting and internal validity (Appendix 3). One reviewer applied the checklist to the identified studies, and these results were checked by a second reviewer.

4.6 Data Synthesis and Analysis

The findings were described qualitatively in planned evidence tables and a structured discussion of collected data. Findings about the impact of including or excluding randomized trials that are reported in LOE are presented. Meta-analyses were not conducted.

4.7 Environmental Scan of Language Policies of HTA Agencies

An environmental scan of policies that are used by HTA agencies in Canada and elsewhere was conducted through an electronic survey. Four questions were asked to each member agency of CADTH's Health Technology Analysis Exchange (a network of Canadian HTA producers[21]). The Health Technology Assessment International (HTAi) Information Resources Group and other HTA agencies that were known to the authors were also contacted.

The questions were:
1. What is your current policy on searching for literature in languages other than English?
2. Do you restrict your reviews to the English language?
3. If you answered "yes" to question 2, at what stage do you restrict it to the English language (literature search, first-level screening, second-level screening, data extraction)?

4. Other information that you would like to provide on this topic that is not addressed by questions 1 to 3.

5 RESULTS

5.1 Quantity of Research Available

In the literature search, 19,482 unique citations were identified across all databases. Of these, 19,352 citations were excluded. Twenty-five citations were judged to be potentially relevant. Upon review of the full text of the 25 citations, where available, 20 citations were excluded because they did not examine the effect of language restriction on the meta-analytic endpoint. Five reports[7,11,22-24] describing three unique studies[11,22,24] were included. The QUOROM flowchart appears in Figure 1, and a list of excluded studies appears in Appendix 4.

5.2 Study Characteristics

Table 1 shows the characteristics of each included study. A description of the primary objective and the associated methods of each study appears in Appendix 5.

5.2.1 Study design

Each of the five reports used a similar approach. Meta-analyses were identified through a literature search and the application of selection criteria. Then, the meta-analytic endpoint of a binary outcome in each identified SR/MA was compared using an odds ratio to the same SR/MA that was reanalyzed after data from RCTs reported in LOE were removed. Bias was then expressed as a summary effect measure across all SR/MAs combined meta-analytically and reported as a ratio of odds ratios (ROR).

5.2.2 Selection criteria

In two studies, SR/MAs were included if they were published in English, if the primary data sources were RCTs, and if the report stated whether only trials in English were eligible for inclusion or whether trials that were reported in LOE were also considered.[11,23] Pham et al. considered systematic reviews that were reported in LOE with at least one report that was written in LOE on the meta-analytic outcomes of interest.[23] Moher et al. considered meta-analyses that included between two and 99 RCTs and reported binary outcomes.[24] Meta-analyses where RCTs that were reported in LOE were excluded, those that included RCTs that were reported in LOE but in which no RCTs that were reported in LOE were used to contribute to the quantitative analysis of the report, and those that included reports that were written in LOE in the quantitative analysis were included.[24] Jüni et al.[11] and Egger et al.[7] included meta-analyses that were based on comprehensive literature searches and provided enough data on the methods to facilitate the replication of the meta-analysis.[7,11]

Figure 1: Selection of Included Studies

27,213 potentially relevant studies identified through electronic search

Excluded 7,731 duplicate records

19,482 records identified (including alerts)

19,352 studies not relevant to systematic review

130 studies requiring more detailed evaluation (screened by title only)

64 studies not relevant to systematic review

66 studies requiring more detailed evaluation (screened by title and abstract)

41 studies not relevant to systematic review

25 full-text articles screened

20 reports did not present pooled results that had been reanalyzed according to language of publication

5 reports included for systematic review

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Table 1: Study Characteristics						
First Author, Country of Origin	**Selection Criteria**	**Databases Searched**	**Search Years**	**Meta-analysis (number), RCTs (number)**	**Non-English Languages Included**	**Disease Areas or Medical Specialties (number)**
Moher,[24] Canada	SR/MA of 2 to 99 RCTs reporting binary outcomes	MEDLINE, CDSR	1966 to 1996	79, NR	Chinese, Danish, Dutch, French, German, Italian, Spanish	Infectious disease (10), circulatory disease (26), pregnancy and childbirth (8), other (35)
Jüni,[11] United Kingdom	Replicable MA of ≥ 5 RCTs with complete search	Hand-searching medical journals, UK NHS R&D HTA, CRD, CDSR	1994 to 1998	50, 600	Chinese, German, French, Italian, Japanese, Spanish, Portuguese, Other	Tobacco addiction (69), obstetrics and gynecology (73), cardiology and angiology (136), infectious disease (137), neurology (54), psychiatry (40), rheumatology and orthopedics (56), other (35)
Egger,[7] Switzerland	Any-language replicable MA with complete search	MEDLINE, EMBASE, CRD, CDSR, UK NHS R&D HTA, hand-searching medical journals	1994 to 1998	60, 783	Chinese, German, French, Italian, Japanese, Spanish, Portuguese, Other	Obstetrics and gynecology (125), cardiology and angiology (144), infectious disease (78), neurology (52), psychiatry (79), rheumatology and orthopedics (63), neonatology (39), gastroenterology (39), oncology (54), other (110)
Moher,[22] Canada	English SR/MA of RCTs with stated language restriction	MEDLINE, EMBASE, CDSR, CISCOM	1985 to 1999	130, NR	Danish, German, French, Italian, Japanese, Portuguese, Spanish	Circulatory disease (37), infectious disease (10), digestive (14), pregnancy and childbirth (12), genitourinary (10), mental health (9), nervous system and sense organs (6), neoplasms (6), respiratory (4), other (22)
Pham,[23] Canada	English-language SR/MA of RCTs with stated language restriction and LOE outcome data	MEDLINE, EMBASE, CDSR, CISCOM	1985 to 1999	42, 662	NR	NR

CDSR = Cochrane Database of Systematic Reviews; CISCOM = Centralised Information Service for Complementary Medicine; CRD = Centre for Reviews and Dissemination; HTA = health technology assessment; LOE = languages other than English; MA = meta-analysis; NHS R&D = National Health Service Research and Development; NR = not reported; RCT = randomized controlled trial; SR/MA = systematic review-based meta-analyses.

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5.2.3 Databases searched

The Cochrane Systematic Review Database was searched for all reports, and MEDLINE was searched for studies in four reports.[7,22-24] EMBASE was searched for three reports.[7,22,23] Jüni et al. and Egger et al. searched by hand for literature published in Health Technology Assessment reports and medical journals (for example, *The American Journal of Cardiology, Annals of Internal Medicine, British Medical Journal, Cancer, Circulation, Journal of the American Medical Association, The Lancet, The New England Journal of Medicine*, and *Obstetrics & Gynecology*). Moher et al.[22] and Pham et al.[23] included the Centralised Information Services for Complementary Medicine as part of the literature search. The included studies were published from 2000 onwards.

5.2.4 Number of studies reviewed

The number of meta-analyses that were included in the reports ranged from 42[23] to 130.[22] The number of RCTs in the meta-analyses ranged from 600[11] to 783.[7]

5.2.5 Languages of studies

The systematic reviews that were included in four of the identified reports considered RCTs that were published in German, French, Italian, and Spanish as part of the review.[7,11,22,24] Other languages include Chinese,[7,11,24] Portuguese,[7,11,22] and Danish.[22,24] In Jüni et al.'s[11] and Egger et al.'s reports,[7] 42 (36.5%) trials were in German, 29 (25.2%) in French, 12 (10.2%) in Italian, eight (7%) in Japanese, seven (6.1%) in Spanish, six (5.2%) in Portuguese, eight (7%) in four other European languages, and three (2.6%) in Chinese. The other reports did not state the proportion of LOE.[22-24]

5.2.6 Disease areas and medical specialties

The disease areas and medical specialties varied across reports. Infectious disease was addressed in four reports.[7,11,22,24] RCTs that were related to circulatory disease were found in two reports,[22,24] and two reports covered the same medical specialties.[11,26] The non-English languages, disease areas, and medical specialties that were included were not stated in one report.[23] Two reports included systematic reviews of complementary and alternative medicine.[22,23] None of the studies provided information on the RCTs or patient population of the included studies.

5.2.7 Country of origin

Three studies were conducted in Canada,[22-24] one study was done in the United Kingdom,[11] and one study was done in Switzerland.[7]

5.2.8 Source of funding

Moher et al. received funding from the Medical Research Council of Canada,[24] and the remaining reports were funded by the National Health Service Research & Development Health Technology Assessment Programme.[7,11,22,23] None of the reports declared a conflict of interest.

5.3 Methodological Quality Assessment

When we used our quality criteria to examine the studies, we found that none of the studies harboured deficiencies in methodological quality (Table 2). Two studies[22,23] reported a sample size power calculation, and one study[23] did not describe the distribution of confounders in the report but did refer to a related report that included this information.

5.4 Data Synthesis and Analyses

5.4.1 Summary treatment effects

None of the included studies found major differences in summary treatment effects when LOE-restricted meta-analyses and LOE-inclusive meta-analyses were compared.[7,11,22-24]

Moher et al.[24] found that language-restricted meta-analyses, compared with language-inclusive meta-analyses, did not differ with respect to the estimate of benefit of the effectiveness of an intervention (ROR 0.98, 95% confidence interval [CI] 0.81 to 1.17). This suggested a 2% difference, on average, between the treatment estimates with or without explicit restrictions on the language of publication of the trials that were included. Language inclusive meta-analysis had narrower CIs (average width 0.79; 95% CI 0.51 to 1.07) compared with language-restricted meta-analyses (average width 0.92; 95% CI 0.53 to 1.32) (relative difference of 16%; P = 0.045).

Egger et al.[7] and Jüni et al.[11] found that treatment effect estimates were approximately 16% more beneficial in trials that were reported in LOE (ROR 0.84; 95% CI 0.74 to 0.97, P = 0.011). There was heterogeneity between meta-analyses (P = 0.003), with pooled effect estimates of non-English-language trials ranging from 90% more to 147% less beneficial compared with English-language trials. The changes in the pooled estimates of individual meta-analyses that occurred when trials that were reported in LOE were excluded from the meta-analyses ranged from a 42% increase (less benefit) to a 22.7% decrease (more benefit) of estimates to treatment effects. In 58% of the meta-analyses, the changes were less than 5%. Among the remaining 21 meta-analyses, five showed more benefit and 16 less benefit after the exclusion of trials that were reported in LOE. The average precision of pooled estimates decreased from 8.34 to 7.68 after the exclusion of trials that were reported in LOE. The authors[7,11] stratified analyses by indication and compared pooled estimates in cardiology and angiology (ROR 0.78, 95% CI 0.64 to 0.94), infectious disease (ROR 0.83, 95% CI 0.68 to 1.00), neurology (ROR 0.68, 95% CI 0.40 to 1.13), obstetrics and gynecology (ROR 1.00, 95% CI 0.61 to 1.65), psychiatry (ROR 0.63, 95% CI 0.39 to 1.02), rheumatology (ROR 1.02, 95% CI 0.80 to 1.30), and tobacco addiction (ROR 0.75, 95% CI 0.50 to 1.13). The extent of overestimation of effect sizes in trials that were reported in LOE (an ROR of less than one) varied by field. Accordingly, the proportion of the total number of studies that were non-English meta-analyses varied from 10.1% (tobacco addiction) and 12.3% (obstetrics) to 35% (psychiatry) and 35.7% (rheumatology). The trials that were reported in LOE contributed an average of 17.5% of the weight in meta-analysis (median 10.2%; range 1.2 to 81.1%).

Pham et al.[23] found that the exclusion of reports that were written in LOE from the meta-analytic part of systematic reviews did not affect the results in conventional medicine. Systematic reviews

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that excluded or included LOE did not introduce bias in terms of estimates of interventions' effectiveness (random effects ROR 1.02, 95% CI 0.83 to 1.26). English-language trials were found to report smaller effect sizes than trials that were reported in LOE in conventional medicine.

Table 2: Quality Assessment of Included Studies						
Domain	**Quality Criteria**	**Study**				
		Moher[24]	**Moher**[22]	**Pham**[23]	**Egger**[7]	**Jüni**[11]
Reporting	Is hypothesis or objective of study clearly described?	Y	Y	Y	Y	Y
	Are main outcomes to be measured clearly described in introduction or methods section?	Y	Y	Y	Y	Y
	Are characteristics of studies that were included in study clearly described (with inclusion and exclusion criteria)?	Y	Y	Y	Y	Y
	Are exposures of interest clearly described?	Y	Y	Y	Y	Y
	Are distributions of principal confounders in each group to be compared clearly described (% LOE RCTs, specialty, year, number of studies)?	Y	Y	N*	Y	Y
	Are main findings of study clearly described?	Y	Y	Y	Y	Y
Validity	Does study provide estimates of random variability in data for main outcomes?	Y	Y	Y	Y	Y
	Have probability values been reported for main outcomes except where probability value is < 0.001?	Y	Y	Y	Y	Y
	Were statistical tests used to assess main outcomes appropriate?	Y	Y	Y	Y	Y
	Were main outcome measures used accurate (valid and reliable)?	Y	Y	Y	Y	Y
	Were studies taken from same population?	Y	Y	Y	Y	Y
	Did study describe a sample size calculation suggesting that it had sufficient power to detect a clinically important effect where probability value for a difference being due to chance is < 5%?	N	Y	Y	N	N

LOE = languages other than English; RCTs = randomized controlled trials.
*Brief narrative description; refers to detailed description in a related article.

5.4.2 Number of included studies and patients

Four[7,11,22,24] included studies summarized the differences in the number of patients and the number of studies in meta-analyses that included studies that were reported in LOE compared with those that did not.

Moher et al.[22] found that the systematic reviews with publications that were written in LOE in their analysis included a higher number of RCTs (median 17; interquartile range [IQR] 9 to 25) and a larger number of participants (median 1,658; IQR 112 to 40,341) than those that were limited to English studies (median 11 RCTs, IQR 6 to 23; median 971 patients, IQR 112 to 52,869). Moher et al.[24] reported medians of nine RCTs per meta-analysis (IQR 6.5 to 18) in language-inclusive reviews, compared with corresponding medians of six studies (IQR 4 to 9.25) in the language-restricted group. Egger et al.[7] noted that trials that were reported in LOE included fewer participants than English-language trials but were more likely to show statistically significant results of P less than 0.05 ($P = 0.033$) and P less than or equal to 0.01 ($P = 0.007$). Jüni et al.[11] reported that English-language RCTs had significantly higher mean (269 ± 487 compared with 147 ± 195; $P < 0.01$) and median (116 compared with 88; $P < 0.01$) sample sizes compared with non-English RCTs.

5.4.3 Methodological quality

Three included reports[11,22,22] discussed the quality of the RCTs in meta-analyses, the quality of the meta-analyses, or both.

Based on the assessment of individual RCTs that were taken from their database of 50 systematic reviews, Jüni et al. found that English-language trials tended to be of a higher methodological quality than those published in other languages.[11] Specifically, 88 English-language reports (35.7%) indicated an adequate concealment of allocation (defined as central randomization, use of coded drug packs, use of assignment envelopes) compared with 12 reports that were written in LOE (25.0%) ($P = 0.15$), and 153 English-language reports (66.5%) were double- or assessor-blinded compared with 23 reports that were written in LOE (46.9%) ($P = 0.016$).[11]

Moher et al.[22] detected minor differences in the quality of reports on RCTs that were reported in English or in LOE. Language-inclusive systematic reviews were of higher quality than language-restrictive reviews, and language-inclusive reviews included more comprehensive searches than language-restrictive reviews.[22] In the analysis, which was based on the Oxman-Guyatt (OG) instrument, language-inclusive reviews were of a higher quality in comparison with reviews that did not search for reports that were written in LOE or searched for reports that were written in LOE but did not include publications that were written in LOE (median OG score for language-inclusive systematic reviews with reports that were written in LOE: four out of seven items; compared with median OG score for language-restricted reviews and reviews that were language-inclusive but did not include publications that were written in LOE: three out of seven items [$P = 0.25$]). Details about the quality assessment were not provided (the overall score was reported instead). Minor differences were detected in the quality of reports in English RCTs compared with those in the eight other languages among which German and French dominated.[27]

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Moher et al.[22] found that there were no statistically significant differences between English RCTs and RCTs that were reported in LOE in terms of likelihood to report a valid approach to patient randomization (90% compared with 83%; P = 0.13), account for patient withdrawals and losses to follow-up (64% compared with 57%; P = 0.43), or report use of double-blinding (57% compared with 50%; P = 0.29). The authors compared the quality scores of RCTs using the Jadad scale. The percentages of low-quality studies (Jadad score 0 to 2; 52% of English RCTs and 60% of RCTs that were reported in LOE) and high-quality studies (Jadad score 3 to 5; 48% of English RCTs and 40% of RCTs that were reported in LOE) were comparable (P = 0.23). Allocation concealment was considered inadequate or unclear in 87% and 96% of the English RCTs and RCTs that were reported in LOE respectively.

5.4.4 Publication status

Two reports[22,23] evaluated the potential existence of publication bias in LOE-restricted meta-analyses, LOE-inclusive meta-analyses but with no LOE contribution to the quantitative analysis, or LOE-inclusive meta-analyses with input into the quantitative summary. Both reports found no major increase in funnel plot symmetry (no major evidence of publication bias) that was associated with the meta-analyses in any of these categories.[22,23]

5.4.5 Statistical heterogeneity

Moher et al.[22] used I^2 to compare the statistical heterogeneity of LOE-restricted meta-analyses, LOE-inclusive meta-analyses but with no LOE contribution to the quantitative analysis, or LOE-inclusive meta-analyses with input into the quantitative summary. The I^2 statistic quantifies the percentage of variation across studies that is due to heterogeneity instead of chance. Between-study heterogeneity is substantial if I^2 is 50% or more. The findings indicated that between-study heterogeneity increased by 2.4% with the inclusion of RCTs that were reported in LOE in 34 conventional medicine systematic reviews. Pham et al.[23] found no significant relationship between restrictions on the language of publication and statistical heterogeneity.

5.4.6 Environmental scan of language policies across HTA organizations

Canadian and international HTA organizations responded to our queries about their language policies. Six of the 10 Canadian HTA organizations do not have a policy on languages or include LOE in the literature searches (with the understanding that articles that are written in LOE may be excluded during first- or second-level screening or during data extraction). A decision to restrict research to English-language-only articles is based mainly on the capabilities of the research staff members, the timelines, and the available resources for translation. Three Canadian organizations restrict the languages to those understood by staff members. One Canadian organization restricts its searches to English because of a lack of resources to pay for translation fees. Twelve of 19 international organizations do not impose language restrictions on the literature search. The policies depended on such factors as the language capacity of staff members and their ability to meet tight deadlines. One organization stated that if articles that are written in LOE are found, they will be translated. Seven international organizations limit their searches to English articles only or to languages in which staff members may be fluent. Appendix 6 gives the details of this survey.

6   DISCUSSION

Five studies that assessed the impact of language of publication on summary treatment effects were selected for our review.[7,11,22-24] None of these reports provided empirical evidence that the exclusion of papers that are written in LOE leads to biased estimates of an intervention's effectiveness when the intervention was conventional medicine.[7,11,22-24] Conflicting findings about the methodological and reporting quality of trials that were reported in LOE compared with English trials were found, and the precision of pooled estimates improved with the inclusion of RCTs that were reported in LOE. These findings do not rule out the potential introduction of language bias when language restrictions are used, so it seems that systematic reviewers of conventional medicine who hope to minimize the risk of producing a biased summary effect estimate should search for foreign language studies.

The studies that are identified in this systematic review show that the extent of influence of studies that are reported in LOE may vary by clinical specialty or disease. Although the primary computation of RORs in several included articles could not be used to identify significant changes in overall pooled measures of effectiveness, stratified analyses showed that the impact of trials that are reported in LOE is heterogeneous across medical specialties and that the number of non-English meta-analyses was greater in some medical specialties compared with others.[11,22,23] More research in medical disciplines to assess the relative impact of trials that are reported in LOE on meta-analytic findings, number of included studies, and number of included patients will reduce the uncertainty about the effect of restrictions in publication language.

This review identified conflicting evidence about the methodological and reporting quality of studies that are published in English compared with those published in LOE. Moher et al.[28,29] detected no differences in the reporting of randomization, double-blinding, dropouts, withdrawals, and allocation concealment. This is noteworthy because Moher et al. previously showed that the poor reporting of these quality measures is associated with exaggerated estimates of intervention efficacy and can bias the outcomes of meta-analysis.[29] On the other hand, Jüni et al.[11] showed that English-language trials were of a higher methodological quality and had better-reported allocation concealment than trials that are reported in LOE. It has been suggested that the conflicting results may have been due to the use of different tools to measure quality and the prevalence of complementary and alternative medicine systematic reviews and meta-analyses in Moher's study population.

The inclusion of studies that are reported in LOE in a systematic review may require other considerations. The issues that pertain to limitations of database coverage have been discussed. Pilkington et al.[30] noted that, despite its reputation as being increasingly Eurocentric in journal coverage compared with MEDLINE, EMBASE had minimal coverage of Russian and Chinese journals, whereas MEDLINE had a better coverage of Russian publications and limited coverage of French and German publications. Nieminen and Isohanni[31] commented on bias against European journals in medical databases and noted that MEDLINE and EMBASE coverage of medical literature that is published in LOE is inconsistent and limited.

Other reports[32-34] have touched on limitations that stem from database coverage. Publication bias, which is the increased likelihood that studies with statistically positive findings will be

published, is a concern because studies have shown differences in rates of positive findings among English studies compared with those that are reported in LOE.[1,35,36] The reduced rate of publication of studies that are reported in LOE has been associated with the peer-review process.[37,38] These and other factors often limit the ability of researchers to include all relevant studies that are reported in LOE in a systematic review.

The environmental scan showed that most HTA organizations do not restrict assessments to English-language reports at the search phase of the review process. LOE policies were typically based on in-house translation capacity.

A limitation of this systematic review is that several included studies were based on collections of systematic reviews from a range of clinical disciplines. None of the included articles focused on a medical specialty. This provides limited evidence of the importance of trials that are reported in LOE in the specialties of interest. Egger et al. have shown how the trials that are published in LOE are important in psychiatry, rheumatology, and orthopedics.[7] Pan et al. have noted that Chinese studies are crucial in molecular medicine.[34] This highlights the need for comprehensive studies of the importance of studies that are reported in LOE in different clinical specialties and regarding specific diseases.

Another limitation of this review is that we did not have a validated instrument to examine the methodological quality of empirical studies. We are unable to comment on the interpretation of the findings from our homemade checklist.

In addition, some of the included studies included meta-analyses where only one or two studies that were reported in LOE were identified. Whether this represents the totality of foreign studies that are available for those meta-analyses or whether a lack of sufficient translation resources for varied languages is responsible for such instances is unclear. Thus, the true "exposure" of meta-analyses to data that are presented in LOE may be limited.

Lastly, EMBASE was not searched in two studies that were included in this review.[11,24] Because the coverage of European journals is greater in EMBASE than in MEDLINE (it indexes more than 4,000 journals from approximately 70 countries[39]), potentially relevant studies may have been missed.

6.1 Generalizability of Findings

The selected studies in this report provide evidence of the impact of language restrictions in a systematic review and meta-analysis on summary treatment effects. We also found evidence of the effect of language restriction on the number of patients, methodological quality, publication status, and statistical heterogeneity. We did not, however, find any studies that were related to other measures associated with language bias that may ultimately affect summary estimates.

The environmental scan of language policies across HTA organizations indicates that most research groups do not restrict the literature searched to English-only articles. If research staff members are not fluent in a language and resources for translation are unavailable, then an article in that is written in LOE is unlikely to be included in the assessment. Based on the list of participating respondents from HTA agencies, these findings can be regarded as generalizable.

6.2 Knowledge Gaps

Given that the selected studies in this report examined the impact of language restriction on summary treatment effect, future research may involve a comprehensive review that measures the impact of other measures that are related to language restriction. These include MEDLINE Index bias, database bias, peer-reviewed bias, and non-indexed journal bias. It is not possible to conclude from this report whether language restrictions can decrease the validity of summary treatment effects in SR/MA. Further evaluation of the importance of language restriction in specific clinical specialties or diseases is needed.

7   CONCLUSIONS

We could not find evidence of a systematic bias from the use of language restrictions in SR/MA of conventional medicine. These findings suggest that more research is needed, particularly in certain medical specialties, to better understand the role of language restriction when performing SR/MA. Language restrictions may be associated with the identification of higher quality RCTs. The inclusion of publications that are written in LOE in systematic reviews may increase the external validity of the report for specific clinical specialties where publications that are written in LOE are known to be influential. These findings do not rule out the potential introduction of language bias when language restrictions are used, so it seems that systematic reviewers of conventional medicine who hope to minimize the risk of producing a biased summary effect estimate should search for foreign language studies when resources and time are available. By avoiding language restrictions, systematic reviewers will have an increased awareness of the number of studies that are reported in LOE and that are available (and respective sample sizes), and readers and future researchers will have an increased ability to assess the limitations of reviews that exclude studies that are reported in LOE.

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APPENDIX 1: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	BIOSIS Previews <1989 to 2007 Week 39>
	CINAHL - Cumulative Index to Nursing & Allied Health Literature <1982 to September Week 1 2007>
	EBM Reviews - Cochrane Central Register of Controlled Trials <3rd Quarter 2007>
	EBM Reviews - Cochrane Database of Systematic Reviews <3rd Quarter 2007>
	EBM Reviews - Database of Abstracts of Reviews of Effects <3rd Quarter 2007>
	EMBASE <1988 to 2007 Week 36>
	Ovid MEDLINE <1966 to September Week 3 2007>
	Ovid MEDLINE In-Process & Other Non-Indexed Citations <September 13, 2007>
	* Note: Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	September 13, 2007
Alerts:	Monthly search updates began Sept 13, 2007 and ran until March 18, 2008
Study Types:	None
Limits:	Publication years 1990-Sept 13, 2007

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
Fs	Floating subheading
Exp	Explode a subject heading
$	Truncation symbol, or wildcard: retrieves plural or variations of a word
*	Indicates that the marked subject heading is a primary topic
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number

BIOSIS Previews STRATEGY

CINAHL STRATEGY

COCHRANE DATABASES

EMBASE STRATEGY	
MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations STRATEGY	

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1950 to Present		
#	**Search History**	**Results**
1	Language$.mp.	17105
2	non-english.ti,ab,sh,hw.	67702
3	english.ti,ab,sh,hw.	1480763
4	loe.ti,ab,sh,hw.	370
5	anglophone.ti,ab,sh,hw.	86
6	non-anglophone.ti,ab,sh,hw.	2
7	or/1-6	1484792
8	"bias (epidemiology)".sh.	1533339
9	Selection bias.sh.	35857
10	Publication bias.sh.	4968
11	or/8-10	155187
12	Publication$.mp.	2500297
13	Unpublish$.mp.	6102
14	Publish$.mp.	302227
15	Report$.mp.	291170
16	Unreport$.mp.	123947
17	Literature.mp	5899
18	or/12-17	3107487
19	7 and 11 and 18	25651
20	limit 22 to yr="1990-2007"	19692

Grey Literature and Hand Searches

Dates for Search:	August 2007
Keywords:	Language bias, Tower of Babel bias, English-language bias, database bias, location bias
Limits:	Publication years 1996-present

* NOTE: This section lists the main agencies, organizations, and websites searched**; it is not a complete list.** For a complete list of sources searched, contact CADTH (http://www.cadth.ca).

Health Technology Assessment Agencies

Alberta Heritage Foundation for Medical Research (AHFMR)
http://www.ahfmr.ab.ca

Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS). Québec
http://www.aetmis.gouv.qc.ca

Canadian Agency for Drugs and Technologies in Health (CADTH)
http://www.cadth.ca

Centre for Evaluation of Medicines. Father Sean O'Sullivan Research Centre,
St.Joseph's Healthcare,Hamilton, and McMaster University, Faculty of Health Sciences. Hamilton, Ontario
http://www.thecem.net/

Centre for Health Services and Policy Research, University of British Columbia
http://www.chspr.ubc.ca/cgi-bin/pub

Health Quality Council of Alberta (HQCA)
http://www.hqca.ca

Health Quality Council. Saskatchewan.
http://www.hqc.sk.ca/

Institute for Clinical Evaluative Sciences (ICES). Ontario
http://www.ices.on.ca/

Institute of Health Economics (IHE). Alberta
http://www.ihe.ab.ca/

Manitoba Centre for Health Policy (MCHP)
http://www.umanitoba.ca/centres/mchp/

Ontario Ministry of Health and Long Term Care. Health Technology Analyses and Recommendations
http://www.health.gov.on.ca/english/prOviders/program/ohtac/tech/techlist_mn.html

The Technology Assessment Unit of the McGill University Health Centre
http://www.mcgill.ca/tau/

Therapeutics Initiative. Evidence-Based Drug Therapy. University of British Columbia
http://www.ti.ubc.ca

Health Technology Assessment International (HTAi)
http://www.htai.org

International Network for Agencies for Health Technology Assessment (INAHTA)
 http://www.inahta.org

WHO Health Evidence Network
http://www.euro.who.int/HEN

Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S)
http://www.surgeons.org/Content/NavigationMenu/Research/ASERNIPS/default.htm

Centre for Clinical Effectiveness, Monash University
http://www.med.monash.edu.au/healthservices/cce/

Medicare Services Advisory Committee, Department of Health and Aging
http://www.msac.gov.au/

NPS RADAR (National Prescribing Service Ltd.)
http://www.npsradar.org.au/site.php?page=1&content=/npsradar%2Fcontent%2Farchive_alpha.html

Institute of Technology Assessment (ITA)
http://www.oeaw.ac.at/ita/index.htm

Federal Kenniscentrum voor de Gezendheidszorg
http://www.kenniscentrum.fgov.be

Danish Centre for Evaluation and Health Technology Assessment (DCEHTA). National Board of Health
http://www.dihta.dk/

DSI Danish Institute for Health Services Research and Development
http://www.dsi.dk/engelsk.html

Finnish Office for Health Care Technology and Assessment (FinOHTA). National Research and Development Centre for Welfare and Health
http://finohta.stakes.fi/EN/index.htm

L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES). Ministere de la Santé, de la Famille, et des Personnes handicappés
http://www.anaes.fr/anaes/anaesparametrage.nsf/HomePage?ReadForm

Committee for Evaluation and Diffusion of Innovative Technologies (CEDIT)
http://cedit.aphp.fr/english/index_present.html

German Institute for Medical Documentation and Information (DIMDI). Federal Ministry of Health
http://www.dimdi.de/static/de/hta/db/index.htm

Health Service Executive
http://www.hebe.ie/ProgrammesProjects/HealthTechnologyAssessment

College voor Zorgverzekeringen/Health Care Insurance Board (CVZ)
http://www.cvz.nl

Health Council of the Netherlands
http://www.gr.nl

New Zealand Health Technology Assessment Clearing House for Health Outcomes and Health Technology Assessment (NZHTA)
http://nzhta.chmeds.ac.nz/

Norwegian Centre for Health Technology Assessment (SMM)
http://www.kunnskapssenteret.no/index.php?show=38&expand=14,38

Agencia de Evaluación de Tecnologias Sanitarias (AETS), Instituto de Salud "Carlos III"/ Health Technology Assessment Agency
http://www.isciii.es/htdocs/investigacion/Agencia_quees.jsp

Basque Office for Health Technology Assessment (OSTEBA). Departemento de Sanidad
http://www.osasun.ejgv.euskadi.net/r52-2536/es/

Catalan Agency for Health Technology Assessment and Research (CAHTA)
http://www.gencat.net/salut/depsan/units/aatrm/html/en/Du8/index.html

CMT - Centre for Medical Technology Assessment
http://www.cmt.liu.se/pub/jsp/polopoly.jsp?d=6199&l=en

Swedish Council on Technology Assessment in Health Care (SBU)
http://www.sbu.se/

Swiss Network for Health Technology Assessment
http://www.snhta.ch/about/index.php

European Information Network on New and Changing Health Technologies (EUROSCAN). University of Birmingham. National Horizon Scanning Centre
http://www.euroscan.bham.ac.uk

National Horizon Scanning Centre (NHSC)
http://www.pcpoh.bham.ac.uk/publichealth/horizon

NHS Health Technology Assessment /National Coordinating Centre for Health Technology Assessment (NCCHTA). Department of Health R&D Division
http://www.hta.nhsweb.nhs.uk

NHS National Institute for Clinical Excellence (NICE)
http://www.nice.org.uk

NHS Quality Improvement Scotland
http://www.nhshealthquality.org

University of York NHS Centre for Reviews and Dissemination (NHS CRD)
http://www.york.ac.uk/inst/crd

The Wessex Institute for Health Research and Development. Succinct and Timely Evaluated Evidence Review (STEER)
http://www.wihrd.soton.ac.uk/

West Midlands Health Technology Assessment Collaboration (WMHTAC)
http://www.publichealth.bham.ac.uk/wmhtac/

Agency for Healthcare Research and Quality (AHRQ)
http://www.ahrq.gov/

Dept. of Veterans Affairs Research & Development, general publications
http://www1.va.gov/resdev/prt/pubs_individual.cfm?webpage=pubs_ta_reports.htm

VA Technology Assessment Program (VATAP)
http://www.va.gov/vatap/

ECRI
http://www.ecri.org/

Institute for Clinical Systems Improvement
http://www.icsi.org/index.asp

Technology Evaluation Center (Tec). BlueCross BlueShield Association
http://www.bluecares.com/tec/index.html

University HealthSystem Consortium (UHC)
http://www.uhc.edu/

Health Economic

Bases Codecs. CODECS (COnnaissances et Décision en EConomie de la Santé) Collège des Economistes de la Santé/INSERM
http://infodoc.inserm.fr/codecs/codecs.nsf

Centre for Health Economics and Policy Analysis (CHEPA). Dept. of Clinical Epidemiology and Biostatistics. Faculty of Health Sciences. McMaster University, Canada
http://www.chepa.org

Health Economics Research Group (HERG). Brunel University, U.K.
http://www.brunel.ac.uk/about/acad/herg

Health Economics Research Unit (HERU). University of Aberdeen
http://www.abdn.ac.uk/heru/

Health Economic Evaluations Database (HEED)
http://heed.wiley.com

The Hospital for Sick Children (Toronto). PEDE Database
http://pede.bioinfo.sickkids.on.ca/pede/index.jsp

University of Connecticut. Department of Economics. RePEc database
http://ideas.repec.org

Conferences and Meetings

Cochrane 1993-2007

Search Engines

Google™
http://www.Google.ca/

Yahoo!®
http://www.Yahoo.com

APPENDIX 2: DATA EXTRACTION FORM

Author:	
Ref ID:	
Publication Date:	
What country was the report conducted in?	
Years the search covered:	
Subject/topic examined:	
Study design:	
# of reports examined:	
Objectives of research qu.:	
Description of methodology:	
Primary outcomes:	
Secondary outcomes:	
Author's conclusions:	
Search strategies used	
Other	

APPENDIX 3: QUALITY ASSESSMENT INSTRUMENT

1. Is the hypothesis/objective of the study clearly described? (Y/N)

2. Are the main outcomes to be measured clearly described in the introduction or methods section? (Y/N)

3. Are the characteristics of the studies included in the study clearly described? (i.e. inclusion/exclusion criteria) (Y/N)

4. Are the exposures of interest clearly described? (Y/N)

5. Are the distributions of principal confounders in each group to be compared clearly described? (i.e. % LOE RCTs, specialty, year, # studies,) (Y/N)

6. Are the main findings of the study clearly described? (Y/N)

7. Does the study provide estimates of the random variability in the data for the main outcomes? (Y/N)

8. Have probability values been reported for the main outcomes except where the probability value is <0.001? (Y/N)

9. Were the statistical tests used to assess the main outcomes appropriate? (Y/N)

10. Were the main outcome measures used accurate (valid and reliable)? (Y/N)

11. Were the studies taken from the same population? (Y/N)

12. Did the study describe a sample size calculation suggesting that it had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is <5%?(Y/N)

APPENDIX 4: EXCLUDED STUDIES

These studies did not include a reanalysis of RCTs.

1.   Grégorie G, Derderian F, Le Lorier J. Selecting the language of the publications included in a meta-analysis: is there a tower of Babel bias? *J Clin Epidemiol* 1995;48(1):159-63.

2.   Egger M, Zellweger-Zähner T, Schneider M, Junker C, Lengeler C, Antes G. Language bias in randomised controlled trials published in English and German. *Lancet* 1997;350(9074):326-9.

3.   Moher D, Fortin P, Jadad AR, Jüni P, Klassen T, Le Lorier J, *et al*. Completeness of reporting of trials published in languages other than English: implications for conduct and reporting of systematic reviews. *Lancet* 1996;347(8998):363-6.

4.   Vickers A, Goyal N, Harland R, Rees R. Do certain countries produce only positive results? A systematic review of controlled trials. *Control Clin Trials* 1998;19(2):159-66.

5.   Victora CG, Moreira CB. North-South relations in scientific publications: editorial racism? *Revista de Saude Publica* 2006;40(Sp. Iss. SI):36-42.

6.   Heres S, Wagenpfeil S, Hamann J, Kissling W, Leucht S. Language bias in neuroscience - is the Tower of Babel located in Germany? *Eur Psychiatry* 2004;19(4):230-2.

7.   Galandi D, Schwarzer G, Antes G. The demise of the randomised controlled trial: bibliometric study of the German-language health care literature, 1948 to 2004. *BMC Med Res Methodol* 2006;6, 2006. Article Number: 30. Date of Publication: 06 Jul 2006.

8.   Pan Z, Trikalinos TA, Kavvoura FK, Lau J, Ioannidis JPA. Local literature bias in genetic epidemiology: an empirical evaluation of the Chinese literature. *Plos Med* 2005;2(12):1309-17. Available: http://medicine.plosjournals.org/archive/1549-1676/2/12/pdf/10.1371_journal.pmed.0020334-L.pdf (accessed 2007 Nov 7).

9.   Jadad AR, Cook DJ, Jones A, Klassen TP, Tugwell P, Moher M, *et al*. Methodology and reports of systematic reviews and meta-analyses. A comparison of cochrane reviews with articles published in paper-based journals. *JAMA* 1998;280(3):278-80.

10.   Egger M, Smith GD. Meta-analysis bias in location and selection of studies. *BMJ* 1998;316(7124):61-6.

11.   Steiner R. 'The Tower of Babel' or 'after Babel in contemporary psychoanalysis'? Some historical and theoretical notes on the linguistic and cultural strategies implied by the foundation of the International Journal of Psycho-Analysis, and on its relevance today. *Int J Psycho*anal1994;75(5-6):883-901.

12. Winkmann G, Schlutius S, Schweim HG. Publikationssprachen der Impact Faktor-Zeitschriften und medizinischer Literaturdatenbvanken (Nachdruck)[Publication languages of Impact Factor journals and of medical bibliographic databanks (reprint)]. *Klin Monatsbl Augenheilkd* 2002;219(1-2):65-71.

13. Sheikh L, Johnston S, Thangaratinam S, Kilby MD, Khan KS. A review of the methodological features of systematic reviews in maternal medicine. *BMC Medicine* 2007;5:10.

14. Loria A, Arroyo P. Language and country preponderance trends in MEDLINE and its causes. *J Med Libr Assoc* 2005;93(3):381-5.

15. Pilkington K, Boshnakova A, Clarke M, Richardson J. "No language restrictions" in database searches: what does this really mean? *J Altern Complement Med* 2005;11(1):205-7.

16. Scholey JM, Harrison JE. Publication bias: raising awareness of a potential problem in dental research. *Br Dent J* 2003;194(5):235-7. Available: http://www.nature.com/bdj/journal/v194/n5/pdf/4809923a.pdf

17. Nieminen P, Isohanni M. Bias against European journals in medical publication Databases [letters]. *Lancet* 1999;353(9164):1592.

18. Reyes H, Kauffmann R, Andresen M. ¿Es la metodología de nuestros trabajos de investigación esencialmente inferior a la de estudios similares en revistas que se publican en inglés? [Is the methodology of our original articles essentially inferior to similar papers published in English-speaking journals?] [editorial]. *Rev Méd Chile* 1998;126(4):361-2.

19. Junker CA. Adherence to published standards of reporting: a comparison of placebo-controlled trials published in English or German. *JAMA* 1998;280(3):247-9.

20. Winkmann G, Schlutius S, Schweim HG. Publikationssprachen der Impact Faktor-Zeitschriften und medizinischer Literaturdatenbanken [Publication languages of Impact Factor journals and of medical bibliographic databanks]. *Dtsch Med Wochenschr* 2002;127(4):131-7.

21. Wogan C. Addressing English-language bias in science: how journals can support authors whose native language is not English. *Sci Ed* 2001;24(2):47.

22. Nylenna M, Riis P, Karlsson Y. Multiple blinded reviews of the same two manuscripts. Effects of referee characteristics and publication language. *JAMA* 1994;272(2):149-51.

23. Shang A, Huwiler K, Nartey L, Jüni P, Egger M. Placebo-controlled trials of Chinese herbal medicine and conventional medicine comparative study. *Int J Epidemiol* 2007;36(5):1086-92.

24. Kovacs FM, Abraira V. Language bias in a systematic review of chronic pain: how to prevent the omission of non-English publications? *Clin J Pain* 2004;20(3):199-200.

APPENDIX 5: DESCRIPTION OF INCLUDED STUDIES

Studies by Jüni *et al.* (2002)[11] and Egger *et al.*[7] examined the overall impact of trials published in LOE on both the combined estimates and subsequent conclusions of published meta-analyses. Meta-analyses of at least five trials with binary outcomes were included. Estimates of treatment effects from trials published in LOE were compared with those published in English only. Fifty meta-analyses with at least one LOE publication were included in the report (n=485 RCTs published in English and 115 RCTs published in LOE). The authors compared English versus LOE RCTs in terms of study quality (blinding and allocation concealment), sample size, and effect sizes. The impact of LOE studies on pooled analyses was evaluated by computing a ratio of odds ratios (RORs) that provided a comparison of meta-analysis of all studies (foreign and English) versus a language restricted meta-analysis. Analysis was performed in several clinical fields, and was presented accordingly.

In 2000, Moher *et al.*[24] investigated whether the exclusion of LOE studies modified the estimate of benefit of the effectiveness of an intervention in a meta-analysis. Meta-analyses were selected for inclusion if the analysis used data from at least two and a maximum of 99 RCTs and if binary outcomes were reported. Logistic regression was used to calculate a ROR and corresponding confidence interval to assess the effect of language of publication on the estimates of an intervention's effectiveness. Meta-analyses were categorized as being either LOE restricted, LOE inclusive but with no actual LOE contribution to the quantitative analysis, or LOE inclusive, where LOE studies provided input into the quantitative summary. Seventy-nine meta-analyses were selected for inclusion, and only 24% (n=19) of the meta-analyses reviewed included LOE publications in the analysis. One meta-analysis was dropped because it did not report any binary outcomes. The remaining meta-analyses had either no language restrictions but did not include LOE trials into a quantitative analysis (n=22), or explicitly excluded such trials from their study (n=38). The authors also compared the median number of randomized trials and median number of participants included in each category of meta-analysis, as well as the median number of patients per included study.

In a 2003 study, Moher *et al.* assessed the effect of language restriction on quality of reporting and reporting characteristics of systematic reviews, and sought to determine whether there was evidence of differences between quality of reporting for conventional medicine and CAM interventions.[22] Only the analysis pertaining to conventional medicine was considered for this systematic review, concordant with the a priori eligibility criteria. The systematic reviews included were categorized as LOE restricted, LOE inclusive but with no actual LOE contribution to the quantitative analysis, or LOE inclusive with input into the quantitative summary. The impact of LOE at the RCT level was assessed with a fixed effects logistic regression model described by Schulz.[25] Differences in treatment effect were measured by adding an interaction term between the treatment (intervention) and systematic review.[22] The ROR of English-language trials versus LOE for each systematic review was computed, and this information was pooled to measure the influence of publication language on the effectiveness estimates for an intervention. A ROR of less than 1.0 for an interaction term suggested that the English-language trials were methodologically inferior and yielded larger treatment effects compared with LOR trials. On the other hand, a ROR greater than 1.0 was associated with smaller treatment effects in English-language trials.[25]

Pham *et al.*[23] performed a sub-analysis of the data collected in Moher *et al.*'s 2003 report[22] to determine whether LOE restrictions impact the estimates of effectiveness for conventional and complementary alternative medicine in systematic reviews. A large dataset of 42 language inclusive systematic reviews (n=662 RCTs) was used. Again, only the findings relating to conventional medicine (34 systematic reviews) are addressed here. The included systematic reviews were categorized in the same manner as by Moher et al[22], above. As in Moher's study, the log ROR of LOE RCTs versus English RCTs was computed for each systematic review to estimate the impact of language of publication on the summary treatment effects.

APPENDIX 6: LANGUAGE PRACTICES AND/OR POLICIES OF HTA ORGANIZATIONS

Canadian HTA Organizations

Canadian Agency for Drugs and Technologies in Health (CADTH), Canada

Current policy on literature searches in languages other than English
CADTH searches broadly with no language restrictions.

Language restriction in research
The quantity and quality of what's published in English, the time and resources to translate, and input from clinical experts are the fundamental drivers for language restrictions. A final decision is made on a case-by-case basis and the exclusion of LOE papers is noted in the report. CADTH is also staffed with reviewers whose first languages range from French, German, Spanish, Italian and Chinese, The methodology and result sections of these reports will be automatically translated and the full report if necessary.

Additional comments
In an effort to obtain a current measure of the number of reports published in LOE 102 Cochrane reviews and 50 CADTH reports were analyzed (issue 3 Cochrane Library 2007 and CADTH reports up to December 2007). Four per cent of CADTH and less than 1% of Cochrane literature searches excluded LOE. Thirty-eight per cent of CADTH reports and 17% of Cochrane reviews actually included LOE papers in their analysis. Approximately 2.5% of the total citations used in the analyses by both CADTH and Cochrane were written in LOE. This demonstrates that in spite of performing non-restrictive language searches, LOE reports still make up a very small percentage of reports that are included in the clinical analyses of systematic reviews and meta-analyses. However, it should be noted that LOE exclusions do not occur at the search execution stage alone. LOE reports can be excluded at numerous points in the systematic review process.

Institute of Health Economics (IHE), Alberta

Current policy on literature searches in languages other than English
At the most basic level of response, when a simple categorical listing of abstracts (i.e. No assessment) is provided to the requester, literature searches are limited to English-language only. Otherwise, none of the literature searches include language restrictions.

Language restriction in research
IHE reviews include literature in languages with which the individual reviewer is proficient. Therefore, literature in French, Chinese, Romanian, and German are sometimes included in the reviews. In general, most reviews tend to be limited to English language literature.

Research stage where language is restricted to English
The non-English language literature tends to be excluded after the screening of abstracts and prior to the retrieval of full-text articles. However, if the abstract appears as though it may have been included in the study if it were in English, the reviewer will note that in the final report.

Evidence-Based Practice Center- University of Alberta, Alberta

Current policy on literature searches in languages other than English
With rare exception, the center does not limit searches by language.

Language restriction in research
If there is no language restriction placed in the literature search, the review is limited only to those studies in languages for which adequate translation services is available to ensure that the studies meet the project's predefined inclusion criteria and that relevant data can be extracted for the review.

Additional comments
It may not be an efficient use of resources to search for non-English studies given both the low yield of non-English studies that pass from screening to the more detailed inclusion/exclusion phase and the empirical evidence that suggests non-English studies may have little impact on summary treatment effects[7,11] and may be of lower quality[7].

Rather than applying a broad policy, the merit of searching for non-English studies within each review is examined and a decision based on additional resources required, level of funding and timelines for a given project, the amount of evidence that exists in English publications, and the clinical area (e.g., complementary and alternative medicine) is made.

Capital Health, Alberta
Current policy on literature searches in languages other than English
When searching for literature in databases, we restrict our search to only include English literature

Language restriction in research
Yes, language restrictions are imposed at the search stage because Capital Health does not currently have the resources to allow for translation of literature from foreign languages.

Alberta Health Technology Assessment Coalition, University of Alberta

Current policy on literature searches in languages other than English
In the past when reviews were funded, non-English speakers were sought after for whatever languages that appeared in the literature searches. This was found to be too time intensive, and, since all HTA reports relate to western medicine topics (lower potential for bias), only languages read by the research team members are included. The languages are: English, French, Spanish, Portuguese, Mandarin, and Italian.

In terms of electronic searching, only databases indexed in English are used; many or all include non-English languages.

Language restriction in research
No, but external translators are no longer sought after.

London Health Sciences Centre, Ontario

Current policy on literature searches in languages other than English
All relevant literature is searched, irrespective of language. If a non-English article fits the inclusion criteria (usually by screening its English abstract), the data will be extracted by one of the many language proficient members of staff within the hospital. If needed, a translator will be contracted, although this is uncommon.

Language restriction in research
No language restrictions exist.

Additional comments
While no language restrictions exist, most reviews end up being restricted to English. There have been a few instances when the non-English literature contributed significantly to results and conclusions.

PATH Research Institute-St. Joseph's Hospital, Ontario

Current policy on literature searches in languages other than English
There are no resources for extensive language conversions.

Language restriction in research
Languages are restricted to English, French and German to match languages spoken in the group.

Agence d'évaluation des technologies et modes d'intervention en santé (AETMIS), Quebec

Current policy on literature searches in languages other than English
AETMIS does not have a formal policy regarding literature searches in languages other than English.

Language restriction in research
No language restrictions exist.

Additional comments
At AETMIS, all literature published in English, French and Spanish are included. Some of the researchers can also read Italian, Portuguese, German, and Danish, so relevant studies in any of these languages may also be included the assessment.

Technology Assessment Unit-McGill University Health Centre-Quebec

<u>Current policy on literature searches in languages other than English</u>
Studies in English and French are commonly searched. Sometimes, if a researcher is fluent in another language, such as Spanish, it may be added to the literature search.

<u>Language restriction in research</u>
No (see above response).

Pharmacy Department-QEII Health Services Centre, Nova Scotia

<u>Current policy on literature searches in languages other than English</u>
The searches are not limited to English, but upon reviewing abstract information,it is very rare that studies are found in languages other than English that the department feels necessary to seek translation.

<u>Language restriction in research</u>
Theoretically no, but the number of studies reviewed in other languages is so small that in reality the reviews are restricted. Also, the reviews are only writen in English.

<u>Research stage where language is restricted to English</u>
If a study was excluded it would most likely be at the first level screening (abstract).

<u>Additional comments</u>
The department' research is confined to drugs. Even though literature searches are not restricted by language, most pertinent drug studies tend to be published in English, even among trials that were conducted in a foreign country. This is likely due to the funding being supplied by Pharmaceutical Companies that publish results in "mainstream" journals. One of the department's reviewers recalls that some trials in Japanese would have been of interest to have translated as, from abstract data, it appeared this population reacted differently to the drugs than those in North American studies (Alpha blocker trials). Translation for these articles was not very feasible.

International HTA Organizations

Faculty of Medicine, Nursing & Health Services, MONASH University, Australia

<u>Current policy on literature searched in languages other than English</u>
Searches are not restricted to English language only - articles in
LOE are filtered out later on in the process

<u>Research stage where language is restricted to English</u>
At the first level of screening.

<u>Additional comments</u>
As we are not proficient in languages other than English and having

articles translated is a cost beyond what our budget can bear, restricting to English language only is practical rather than scientifically desirable. In the light of making systematic reviews and HTAs as widely encompassing of the scientific literature as the
process aims to be, it would be of great assistance if there were translating agencies that charged reasonable costs and/or publishers translated individual articles on demand for a slightly increased pay-per-view fee.

Genetics & Health Technology Programs Branch-Department of Human Services, Australia

Current policy on literature searched in languages other than English
No explicit policy exists, but this is a default approach given the workload of staff members. There is, however, in-house capacity to review evidence published in French, Italian and Spanish.

Language restriction in research
Please see response above (i.e. essentially yes).

Research stage where language is restricted to English
Language restrictions may occur at the literature search stage, during the first or second level screening or data extraction phase.

Additional comments
Australia is generally considered to have a multicultural society, and this is the case in Victoria. However, the majority of the population and health care providers have English as a first language and this drives identification of English language articles. Providers are resourced to translate patient information regarding treatment at the site of service delivery.

IMS Health, Australia

Current policy on literature searches in languages other than English
Literature searches are designed to identify all relevant studies, regardless of language. This includes searches employing the EMBASE.com platform, HTA agency websites, and citation list checking.

Language restriction in research
Reviews are not restricted to English language articles. However, inclusion and translation of non-English literature is usually determined by the value of the article in relation to the research questions. Relevant foreign language articles will be considered for inclusion and translated where necessary: For example, where evidence (in English articles) relating to a particular technology is not available or very limited and/or poor quality. Even where evidence in English is available, foreign language articles that may be pivotal (based on English abstract) will be translated. The inclusion of LOE articles depends on the availability and quality of evidence available in English.

Additional comments
Given the general need for HTA to address questions of safety, effectiveness and cost-effectiveness in an efficient and timely manner, inclusion/translation of LOE articles can

increase the amount of time required for a review and slow-up the process. This has the potential to delay access to beneficial services (where HTA serves to inform patient access/government reimbursement). In addition, HTA agencies may have no or limited resources available to translate potentially relevant articles. Therefore it may not be possible to present detailed evidence from relevant foreign language articles.

National Health and Medical Research Counil (NHMRC) Clinical Trials Centre, Australia

Current policy on literature searches in languages other than English
The procedure adopted by the CTC is not to restrict literature searching to English language publications.

Language restriction in research
Yes, but not unconditionally. Where a non-English language publication is identified which provides a higher level/quality of evidence than that available in the English language literature, then the publication is included and professional translation is undertaken. Where non-English language publications provide an equivalent or lower level/quality of evidence than English language publications, they are excluded. This is considered a pragmatic approach to managing timelines and costs, since professional translation has the potential to add significantly to the timelines and cost of the assessment.

Research stage where language is restricted to English
Non-English language publications are typically excluded at first level screening. Where it is possible to determine at first level (abstract only) screening that a non-English publication provides a lower level/quality of evidence than included studies published in English, language restriction will take place at this stage. If this is not possible, this will occur at second level screening. Often, it is uncertain whether a study is or is not published in English; in such circumstances, decisions about inclusion or exclusion necessarily occur after retrieval of the full publication (second level screening).

Finohta, Finland

Current policy on literature searches in languages other than English
Language restrictions are not applied during the literature search. Staff members are quite talented in languages. In fact, twelve languages are understood in the office (Swedish, Norwegian, Danish, English, French, Spanish, Russian, Estonian, Czech, Italian and even Swahili). A translator has been used, if necessary.

Language restriction in research
Yes, there have been occasions when some articles in other languages have been left out. That has happened while working on a rapid review and the schedule has been very tight; however this is quite rare.

Research stage where language is restricted to English
Language restriction may occur at the article selection stage.

Israeli Center for Technology Assessment in Health Care, Gertner Institute for Epidemiology & Health Policy Research, Israel

Current policy on literature searches in languages other than English
No limitations are placed on the initial search.

Language restriction in research
Reviews are limited to Hebrew and English. Information in other languages may be consulted if pertinent.

Health Technology Assessment Unit, A Gemelli Teaching Hospital, Italy

Current policy on literature searches in languages other than English
Literature searches are usually based on English, Italian, French and to a lesser extent, German articles. Preference is given to English and Italian literature. If a topic relates specifically to a national policy or practice, only Italian literature will be used.

Language restriction in research
All language restrictions are made at the second level of article screening, not during the search

Community & Public Health-Canterbury District Health Board, New Zealand

Current policy on literature searches in languages other than English
Usually all languages are included at the search stage for a systematic review. The language is restricted to English for a Technical Brief.

Language restriction in research
Yes, unless there is a non-English article (or other document) that provides information unavailable in English.
Research stage where language is restricted to English
Reviews are restricted to English during the first or second level screening. This depends on the availability and potential usefulness or volume of available literature on the topic.

Health Services Research and Evaluation-Ministry of Health, Singapore

Current policy on literature searches in languages other than English
To date, literatures searches are not limited by language.
Language restriction in research
No, it depends on the research topic. If it is mainly documented in foreign languages, the articles will be translated to English.

Basque Office for Health Technology Assessment-Basque Government, Spain

Current policy on literature searches in languages other than English
Languages included are Spanish, French, English, Italian, Portuguese, and German.

Language restriction in research
There are no language restrictions. It is impossible to do so if the organization wanted to make contextualization.

Additional comments
The Basque Office has found in some cases invaluable information that is impossible to obtain if literature searches are restricted to English language only documents. Moreover, some inaccurate recommendations in some HTA documents may not consider a search in other languages or discard documents with an abstract only in English.

Southampton Health Technology Assessment Centre (SHTAC)-University of Southampton, United Kingdom

Current policy on literature searches in languages other than English
It is generally SHTAC's policy to restrict all searching to English language (it is written into the protocol) - unless the unit is specifically simultaneously undertaking a report which is also updating a Cochrane report, in this instance it would have to include foreign language papers.

Health Services Research Unit-University of Aberdeen, United Kingdom

Current policy on literature searches in languages other than English
Normally, literature searches are not restricted to English.

Language restriction in research
Usually, reviews are not restricted to the English language unless there are a small number of studies or a substantial proportion of the studies reported in a foreign language.

Research stage where language is restricted to English
Language restrictions apply at the first level screening if there is a large evidence-based in English or at the second level screening for full-text papers retrieved and assessed if smaller evidence-base or if apparently key papers are in a foreign language. In the latter case, the list of studies excluded because they were written in non-English language would be listed in the appendix.

Department of Public Health-University of Birmingham, United Kingdom

Current policy on literature searches in languages other than English

The department's policy is not to apply language restrictions during a literature search.

Language restriction in research
No.

York Health Economics Consortium Ltd.-University of York, United Kingdom

<u>Current policy on literature searches in languages other than English</u>
Studies in languages other than English are part of the literature search, but rarely obtain full copies or abstract them because of resource constraints. The existence of such studies is highlighted in the report.

<u>Language restriction in research</u>
Usually yes.

<u>Research stage where language is restricted to English</u>
Language restriction may occur at any stage, but most often during data extraction.

Department of Primary Health Care-University of Oxford, United Kingdom

<u>Current policy on literature searches in languages other than English</u>
Literature searches are conducted without restriction of languages.

<u>Language restriction in research</u>
There are no language restrictions.

Agency for Healthcare Research and Quality (AHRQ), USA

<u>Current policy on literature searches in languages other than English</u>
AHRQ does not have a standing policy for searching for literature in languages other than English. For each review, the Evidence-based Practice Centers (EPC), with input from technical experts and AHRQ staff, determine inclusion and exclusion criteria based on the key questions. The EPC may decide to exclude non-English studies if appropriate for that particular question. In determining whether to include or exclude non-English studies, the agency considers the adequacy of English language literature and potential bias from excluding non-English studies. For example, excluding non-English studies for a review on bariatric surgery may be justified, whereas excluding non-English studies for a review on ayurvedic and herbal medicine may not. EPCs routinely conduct preliminary literature searches which allow them to make informed decisions about the potential risks of excluding non-English studies as well as the adequacy of literature without non-English studies.

<u>Language restriction in research</u>
AHRQ does not necessarily restrict reviews to English language, although there may be instances where this is done.

<u>Research stage where language is restricted to English</u>
If non-English language is determined to be an *a priori* exclusion criteria, then it would be excluded at the literature search stage as well as at the abstract or full-article level screening whenever a study is identified as non-English.

Drug Effectiveness Review Project (DERP), USA

<u>Current policy on literature searches in languages other than English</u>
Searches are limited to English language.

<u>Language restriction in research</u>
Yes.

<u>Research stage where language is restricted to English</u>
Reviews are restricted to English language at the search stage, and beyond, if any make it through.

<u>Additional comments</u>
In earlier reviews, DERPs policy was to screen LOE articles that had English abstracts. These would be included if they provided unique material. If they did provide something new, these papers would be translated. However, over the years it was noted that they were not translating relevant LOE papers and the volume of literature per report was expanding beyond capacity to maintain this policy, so it was dropped.

ECRI Institute, USA

<u>Current policy on literature searches in languages other than English</u>
Time and budget constraints typically limit searches to English.

<u>Language restriction in research</u>
Yes, 95% of the time.

<u>Research stage where language is restricted to English</u>
Language restrictions occur at the literature search stage and first level screening.

Hayes Inc., USA

<u>Current policy on literature searches in languages other than English</u>
The initial literature search is restricted to English, German, French and Dutch language articles. Articles in German, French and Dutch are only included if they report on clinical trials of equal or better quality than the best available evidence published in English. Articles are also included if the study could impact the conclusions of the health technology assessment. The following languages are also offered on an as-needed basis, if the evidence from these studies would influence the conclusions of our report. These languages are Italian, Spanish, Arabic, and Mandarin; however, they are not routinely selected for detailed review.

<u>Language restriction in research</u>
Languages are restricted to English, Dutch, German, and French.

<u>Additional comments</u>
The foreign language team consists of three senior, PhD-level, medical research analysts whose native languages are German and Dutch. All three scientists speak French as a second language. One of these analysts currently resides in Paris. The two scientists whose native language is Dutch also speak German, in addition to French. Our internal resources regarding other languages are limited; therefore, only chose languages for which they have sufficient capacity are chosen. The remaining languages (Italian, Spanish, Arabic, Mandarin) are covered by only one person each and, subsequently, are not routinely included in our literature search