Comparing Literature Review Requirements for Reimbursement Submissions Across the Globe

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BACKGROUND AND OBJECTIVES

- Rigorous systematic literature reviews (SLRs) are common requirements within national health technology assessment (HTA) reimbursement submissions globally.
- No national HTA agency exists in the United States (US); however, the Academy of Managed Care Pharmacy (AMCP) guidelines[1] are generally used as standard guidance for submissions to payers within the US.
- We compared literature review requirements for reimbursement submissions in Europe, Canada, Australia, and the US.

METHODS

- Submission guidance from eight national HTA agencies—the National Institute for Health and Care Excellence (NICE; England and Wales),[2] Scottish Medicines Consortium (SMC; Scotland),[3] National Centre for Pharmacoeconomics (NCPE; Ireland),[4,5] National Authority for Health (HAS; France),[6-8] Federal Joint Committee (G-BA; Germany),[9] Dental and Pharmaceutical Benefits Agency (TLV; Sweden),[10,11] Canadian Agency for Drugs and Technologies in Health (CADTH, Canada),[12,13] Pharmaceutical Benefits Advisory Committee (PBAC; Australia)[14]—and the AMCP Format for Formulary Submissions (US)[1] were reviewed from their respective websites in March 2018.
- SLR requirements are summarized and compared.

RESULTS

Submission Requirements

- Table 1 presents a summary checklist comparing the submission requirements for each of the nine national bodies investigated.
- The AMCP guidelines, which are specific to the US, do not require or provide any guidance regarding a rigorous SLR with a replicable protocol for clinical or economic evidence. The AMCP format suggests it is the manufacturer's responsibility to define objective criteria for study selection, and to explain the exclusion of specific evidence via a search strategy or CONSORT diagram.
- The Institute for Clinical and Economic Review (ICER) in the US assesses the clinical effectiveness and value of drugs; currently, its decisions are not linked to payers, but it may have a similar role as an HTA in the future.
- Table 2 and Table 3 provide more detail on the requirements for clinical systematic reviews for reimbursement submissions to each national agency. Table 4 provides detail on the requirements for economic reviews (including economic models, utilities, and cost and resource use) for agencies that provide guidance on these requirements (i.e., NICE, HAS, NCPE, and SMC).
- TLV requires only a clinical SLR for indirect comparisons if no head-to-head trials are available between the technology evaluated and the standard comparator(s).
- Canada does not require manufacturers submit an SLR of the clinical evidence as part of a submission dossier; the CADTH clinical reviewers conduct a systematic review of clinical trials as part of their dossier review. However, for oncology drug reviews that are submitted by Provincial Advisory Groups (PAG) or Tumour Groups (TG), an SLR may be provided, the submitters should ensure that they have attempted to systematically identify all available clinical information within the scope of the submission.
- In its guide to the methods of technology appraisal (2013), NICE states that an SLR of relevant studies of the technology being appraised should be conducted according to a previously prepared protocol to minimize the potential for bias. In exceptional circumstances, an SLR may not be necessary.
- Agencies that require a clinical SLR for a reimbursement dossier (PBAC, NICE, HAS, G-BA, NCPE, and SMC) also require a critical appraisal of the included studies, and tools for assessing risk of bias are proposed.
- HAS and NICE require both an SLR and a critical appraisal of existing economic evaluations for the intervention of interest; NICE requires providing sufficient search details so that methods can be reproduced. The date span for the searches should be appropriate, and results should be as current as possible.
- PBAC recommends presenting literature search results for economic evaluations that involve the proposed and similar medicines, as well as any additional literature on utility studies.
- NICE, NCPE, and SMC also require an SLR of cost and resource use data; cost data should be the most recent available, with retrospective input costs updated with the appropriate Consumer Price Index for Health. Only NICE and NCPE specify the need for an SLR of utility data.

CONCLUSIONS

- Requirements for literature reviews for reimbursement submissions vary globally.
- Although most national HTA agencies require rigorous clinical SLRs for reimbursement dossiers, within the US, manufacturers generally define the inclusion/exclusion criteria for clinical and economic evidence submitted for review to payers.
- In order to gain efficiencies, clinical SLRs intended for use across several markets should be conducted in line with the most prescriptive guidance (i.e., G-BA, HAS, and NICE). However, quality assessment/risk of bias guidance for clinical data varies between agencies, with the G-BA requiring the most detailed assessment.
- Fewer agencies require SLRs of economic models, health care resource used, and cost and utilities for reimbursement dossiers.
- Agencies requiring SLRs of utilities, costs, and resource use state that the data should be representative of their population. Therefore, achieving efficiencies in collecting economic and utility data to use across countries may not be possible.

REFERENCES

Please see handout for complete reference list.

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Table 1. Overview of SLR Requirements for Reimbursement Submission to National HTA Agencies and Payers

Submission Requirement	Australia PBAC	Canada CADTH	England and Wales NICE	France HAS	Germany G-BA	Ireland NCPE	Scotland SMC	Sweden TLV	US AMCP
SLR of clinical data for the technology and its comparators	✓	✓ for new oncology drugs	✓	✓	✓	✓	✓	✓ if no head-to-head trials available	✗
Critical appraisal of RCTs and non-RCTs	✓	✗	✓	✓	✓	✓	✓	—	✗
SLR of economic models for technology	✗	✗	✓	✓	—	✗	✗	—	✗
Critical appraisal of economic models	✗	✗	✓	✓	—	✗	✗	—	✗
SLR of health care resource use and cost	✗	✗	✓	—	—	✓	✓	—	✗
SLR of utility data	✗	✗	✓	✗	—	✓	✗	—	✗

✓ = required; ✗ = not required; — no guidance provided.
RCT = randomised controlled trial.

Table 2. Comparing Clinical SLR Requirements for Reimbursement Submissions to National HTA Agencies

Type of Methodology	Australia (PBAC)	Canada (CADTH)	England and Wales (NICE)	France (HAS)
Search strategy and literature search	Include search terms for study design, population, intervention, and comparators (exclude outcomes); record date searched, date span, and details of search. Databases and sources: Medline, Embase, and Cochrane, ClinicalTrials.gov, international clinical trials registry, Australian clinical trials registry, other sources. Use Cochrane guidance for systematic reviews.	If the submitter of an oncology submission is a PAG or TG, an SLR of clinical information may be provided. For all submissions, search strategies, search terms used (i.e., MeSH headings and keywords) and the names of databases (e.g., Medline, Embase, Cochrane) searched are required. Search results are not required. A signed declaration that all known unpublished clinical studies have been disclosed using the Letter Confirming Disclosure of all Known Unpublished Studies template is required.[a]	Describe search strategies used. Follow CRD's 2009 guidance. Provide sufficient detail to enable the methods to be reproduced (e.g., sources and the full electronic strategies for all databases, including any limits applied).	Clear, reproducible search strategy, using explicit selection criteria. Date span of search must be appropriate (see Institute of Medicine [2011] guidance). Source (including French databases): Medline, Embase, Cochrane, HealthSTAR, PASCAL. A list of journals is recommended for systematic searches of tables of contents over the last 6 months; additional references by specialty and relevant websites should be considered.
Selection of studies	Exclude studies based on PICOS: study design, intervention, population and comparator. Complete PRISMA flowcharts for: RCTs for direct comparison, RCTs for indirect comparisons, and nonrandomized studies if no RCT was identified.	For SLRs of oncology submissions conducted by PAG or TG, a tabulated list of all published and unpublished studies must be provided. If these studies are not identified with the support of the manufacturer, unpublished studies should be identified through clinical trial registries.	Describe inclusion and exclusion criteria (PICOS and language restrictions). Prepare PRISMA flow diagram and a log with excluded studies with reasons for exclusion. Follow CRD (2009) guidance. Records assessed by ≥ 1 reviewers increase validity; the procedure for resolving disagreements should be reported.	Follow Institute of Medicine (2011) guidance: 2 reviewers, use of predefined form, double data extraction.
Critical appraisal of RCTs and non-RCTs or risk of bias assessment	Assess risk of bias (internal validity) for RCT as described in chapter 8 of the Cochrane handbook.[b] Discuss unmasking, treatment and testing decisions, and nature of outcomes. Also assess risk of bias of included nonrandomised studies and describe the approach.[c]	Not required	For parallel RCTs, 8-question minimum criterion is proposed. For randomized crossover or cluster trials, and for non-randomized trials, follow CRD's 2009 guidance.	Review each article according to the principles of critical appraisal using checklists.

CRD = Centre for Reviews and Dissemination; PICOS = population, intervention, comparators, outcomes, study design; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
Sources: Australian Government Department of Health and Ageing,[14] CADTH,[12,13] HAS,[6-8] NICE,[15] CRD,[16] Institute of Medicine.[17]
[a] This declaration may be waived if the manufacturer is not involved in the submission.
[b] Cochrane Handbook for Systematic Reviews of Interventions, Version 6, 2018.
[c] The Risk Of Bias In Non-randomized Studies–of Interventions (ROBINS-I) is an alternative approach (it is not necessary to complete the ROBINS-I tool).

Table 3. Comparing Clinical SLR Requirements for Reimbursement Dossiers to National HTA Agencies (Continued)

Type of Methodology	Germany (G-BA)	Ireland (NCPE)	Scotland (SMC)	Sweden (TLV)
Search strategy and literature search	Databases: Medline, Embase, Cochrane (optional: CINAHL, PsycINFO). For each database, include search strategies set up in blocks, separately according to indication, intervention, and possibly study types. Use current validated filters if the strategies are restricted to certain study types (e.g., RCTs). Search registries such as ClinicalTrials.gov, the EU Clinical Trials Register, Clinical Trials PharmNet.Bund, the International Clinical Trials Registry Platform search portal. Optional: Specific study registers or registers of pharmaceutical companies.	SLR conducted and reported according to PRISMA guidelines using a clear protocol and including search strategies for all databases; review peer-reviewed, grey literature, and relevant unpublished data.	Databases searched and literature searching strategies should be reported, including any limits and filters applied. Follow PRISMA checklist for indirect or mixed treatment comparison.	Conduct if no direct evidence available for indirect comparisons. Follow PRISMA checklist.
Selection of studies	Describe the procedure for selecting relevant studies from the results of the search steps. Justify the procedure if the selection was not carried out by two reviewers independently of each other.	Clearly define the inclusion and exclusion criteria (specify restrictions used such as language, population, year); justify any deviation from PICOS; provide a flowchart of the selection process and a list of excluded with reasons for exclusion. For best practices, ≥ 2 reviewers should be used.	Include inclusion/exclusion criteria (according to PICOS), PRISMA diagram, and list of included/excluded articles. Follow PRISMA checklist.	Follow PRISMA checklist.
Quality assessments of comparator RCTs	Assess bias at: • Study level: Randomization, allocation concealment, time parallelism (nonrandomized), comparability of the groups (nonrandomized), blinding, result-controlled reporting, and others. • Endpoint level: Blinding, implementation of intent to treat principle, result-controlled reporting, and others.	Recommended using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.	Each study meeting the criteria for inclusion should be subjected to critical appraisal; specific tool not provided.	Follow PRISMA checklist.

CINAHL = Cumulative Index to Nursing and Allied Health Literature.
Sources: SMC,[3] Higgins and Green,[18] The Dental and Pharmaceutical Benefits Agency (TLV),[10,11] NCPE,[4,5] HIQA,[19,20] IQWiG,[21] G-BA.[9]
AMCP guidance is not presented in this table because AMCP does not provide guidance on SLR requirements for clinical studies.

Table 4. Comparing Economic SLR Requirements for Reimbursement Dossiers to National HTA Agencies

Type of Methodology	NICE	HAS	NCPE	SMC
Literature search of economic models for technology under assessment	Describe strategies used to retrieve relevant cost-effectiveness studies. Provide sufficient detail to enable the methods to be reproduced and the rationale for any inclusion and exclusion criteria used.	Clear, reproducible search strategy, using explicit selection criteria. Date span of search should be appropriate (see Institute of Medicine [2011] guidance).	Not required; economic evaluations may be run alongside a clinical trial rather than data from multiple trials or gathered in a systematic review.	Not required
Critical appraisal of cost-effectiveness evaluations	Use appropriate and validated instrument, such as those of Drummond and Jefferson (1996) or Philips et al. (2004).	Use Drummond and Jefferson (1996) checklist for economic evaluations; use Weinstein et al. (2003) checklist for assessing quality of models.	Not required	Not required
Literature search of cost and resource use data	Include the search strategy and inclusion criteria, and consider published and unpublished studies.	No guidance	Evidence should be presented to demonstrate that the data for resource use and costs have been identified systematically; only direct costs for the most recent calendar year from the health and social system in Ireland should be used.	Evidence should be presented to demonstrate that resource use and cost data have been identified systematically.
Literature search of utility data	Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. Consider published and unpublished studies, including any original research commissioned for the technology.	If no French utility scores are available, international utility data can be used, preferably from a single source. Additional sources can be used in sensitivity analyses.	Transparent, systematic search to obtain published utility values. Justify choice of data and describe methods used. If several options are available, explore uncertainty by sensitivity analysis.	Ideally, utility data will be generated from RCTs, although utilities derived from observational trials are acceptable if they can match those in clinical studies. If utility values are taken from the literature, the literature selection process should be reported.

Sources: NICE,[15] Drummond and Jefferson,[22] Philips et al.,[23] Weinstein et al.,[24] SMC,[3] NCPE,[5] HIQA,[19,20] HAS,[6-8] Institute of Medicine.[21]
AMCP, PBAC, G-BA, TLV, and CADTH guidances are not presented in this table because they do not provide guidance on any economic, utility, or cost and resource use systematic reviews.
IQWiG provides guidance for economic requirements in their General Methods. Version 5.0 publication (available in German only); however, this is not a part of the AMNOG dossier, and it is used only when price negotiations break down.

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