# A Comparison of Health Technology Assessment (HTA) Requirements for Systemic Literature Reviews (SLRs)

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## BACKGROUND

- A systematic literature review (SLR) is a key step in establishing the existing evidence to make informed health technology assessments (HTAs). A well-conducted SLR provides a comprehensive, transparent, and high-quality synthesis of the evidence.
- An SLR is a fundamental component of pharmaceutical manufacturer submissions for many HTA agencies.
- While there is a broad consensus among HTA agencies that an SLR is essential to identify relevant data, the formal requirements to be incorporated in HTA submissions differ among HTA agencies. For example, specific guidance on data sources, methodology, required outcomes, and reporting of the SLR varies considerably between HTA agencies.
- For manufacturers preparing for HTA submissions in multiple markets, it is more cost efficient to design 1 SLR that will meet the requirements for all planned submissions. Conversely, if the HTA bodies of the intended markets do not have stringent SLR guidelines, the additional cost and time associated with the strict guidelines can be avoided.

## OBJECTIVE

- The objective of this research was to review and compare guidance from several prominent HTA organizations across the world for specific requirements related to SLRs.

## METHODS

### Data Source

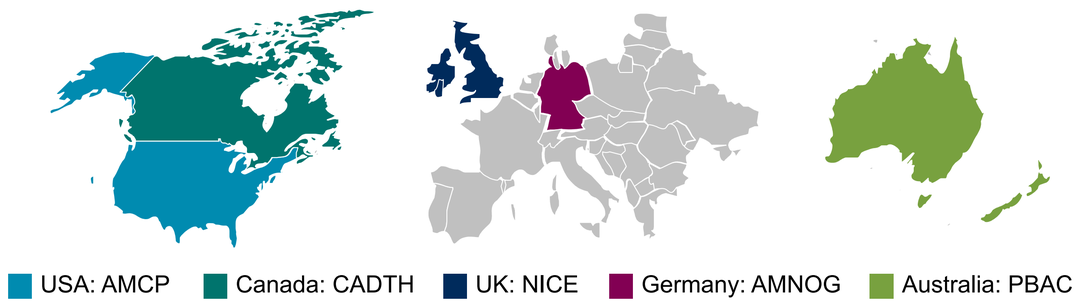
- A convenience sample of 5 prominent HTA agencies was selected to provide a comparison of SLR criteria in key markets of interest to global manufacturers. Those agencies include:
  I. Gemeinsamer Bundesausschuss (G-BA) (per the Act on the Reform of the Market for Medicinal Products [AMNOG] requirements) in Germany[1]
  II. The Academy of Managed Care Pharmacy (AMCP) in the United States[2]
  III. The National Institute for Health and Care Excellence (NICE) in the United Kingdom[3,4]
  IV. The Pharmaceutical Benefits Advisory Committee (PBAC) in Australia[5];
  V. The Canadian Agency for Drugs and Technologies in Health (CADTH)[6-8]
- Searches of these 5 HTA agency websites were performed in June 2017 to identify guidance or requirements for conducting SLRs used in product submissions. These sources were reviewed specifically for guidance related to the submission of clinical, economic, and prevalence data, as well as any requirements related to systematic searches of registry data sources.
  I. Available relevant guidance was hand-extracted and compared between HTA bodies.

## RESULTS

### Countries of interest and HTA agencies (Figure 1)

- All reviewed HTA websites and guidance documents included information regarding the type of literature review needed to provide evidence for the proposed intervention (**Table 1**).
- HTA submission requirements for SLRs generally fell within 3 categories of data: epidemiology (incidence and prevalence of the disease), clinical (for the drug under review and relevant comparators), and economic (economic models, cost, utilization, and utility data) for the drug under review.
- SLRs are mandatory for submission of clinical data in Germany, the UK, and Australia. In Canada, an SLR is not specifically required, but search strategies are required for the submission of clinical data. SLRs are required for the submission of economic data in the US (economic models only) and the UK.
- None of the 5 agencies requires SLRs for the submission of epidemiology data. Hence, efficiencies can be gained by using a targeted literature review approach to gather appropriate epidemiology data for an HTA submission in these countries.

**Figure 1. Countries of Interest and HTA Agencies**




Key: AMCP – Academy of Managed Care Pharmacy; AMNOG – Arzneimittelmarkt-Neuordnungsgesetz; CADTH – Canadian Agency for Drugs and Technologies in Health; HTA – health technology assessment; NICE – National Institute for Health and Care Excellence; PBAC – Pharmaceutical Benefits Advisory Committee; UK – United Kingdom; USA – United States America.

**Table 1. Requirements for Systematic Literature Search in HTA Submissions**

| | Germany (AMNOG) | USA (AMCP) | UK (NICE) | Australia (PBAC) | Canada (CADTH) |
|---|---|---|---|---|---|
| Epidemiological Data | ✓ | ✓ | ✓ | ▪ | ▪ |
| Clinical Data | ┼ | ▪ | ┼ | ┼ | ▪ |
| Economic Data | ▪ | ┼[a] | ┼ | ✓[b] | ▪ |

┼ – SLR is mandatory; ✓ – data are needed but no formal requirements for literature searching; ▪ – no guidelines or requirements reported regarding literature reviews.
[a] SLR required for economic modeling only (Section 4.0).
[b] A review of the literature for relevant economic references is required, although the review is not specified as systematic.
Key: AMCP – Academy of Managed Care Pharmacy; AMNOG – Arzneimittelmarkt-Neuordnungsgesetz; CADTH – Canadian Agency for Drugs and Technologies in Health; HTA – health technology assessment; NICE – National Institute for Health and Care Excellence; PBAC – Pharmaceutical Benefits Advisory Committee; UK – United Kingdom; USA – United States of America.

### SLR Requirements by Topic

**Epidemiology data**

- While all of the included agencies request background information on the intended patient population, none requests an SLR or formal searching on epidemiological evidence.
- The apparent goal of the epidemiology data to be included in submissions is generally to describe the country-specific population anticipated to be treated by the drug under review.
- Although no databases were specified for searches of epidemiological evidence, PBAC does provide a list of sources where data can be obtained to estimate the utilization of products within a population.

**Clinical data (Table 2)**

- Australia, Germany, and the UK require an SLR of clinical data on the efficacy and safety of the product in the proposed indication.
  1. HTA submission guidance in these 3 countries also explicitly mentions inclusion of comparator data and the potential need for indirect treatment comparisons for relevant clinical outcomes.
- NICE and AMNOG provide a scoping document prior to sponsor submission that identifies the relevant comparator(s) and patient populations that should be included.
- One of the recognized challenges is the time lag between initiation of the submission and the availability of clinical evidence. To ensure that the most current clinical data are available for authorities, 2 agencies explicitly request that manufacturers update their SLRs of the clinical data. AMNOG requires the most recent updates before submission (3 months prior to submission).
- All 3 agencies that require an SLR of the clinical data provide detailed guidance mandating specific methodology. In addition, the methods used by the sponsor should be documented in a way that allows for reproducibility of both the searches and the screening process used to identify the relevant literature.
  1. The search protocol should be established ahead of time, including inclusion and exclusion criteria. Rationale for inclusion and exclusion of each identified study should be documented.
  2. NICE provides guidance on the data to be extracted from individual studies; quality assessment is also required (see below).
  3. AMNOG restricts the SLR to evidence against an agency-specified comparator, either head-to-head or for an indirect comparison; AMNOG and PBAC further specify data sources for the review.
- CADTH does not have a formal SLR requirement (ie, not a submission checklist requirement), nevertheless:
  1. For non-oncology products, CADTH's Common Drug Review (CDR) conducts its own SLR.
  2. For oncology products, CADTH's pan-Canadian Oncology Drug Review (pCODR) indicates that the submitter should attempt to systematically identify all available clinical information; SLRs conducted within Provincial Cancer Agencies may be provided as a component of the clinical information supporting efficacy, effectiveness, and safety evidence.
  3. Both CDR and pCODR request documentation of search strategies.

**Economic data (Table 3)**

- Economic data are required by AMCP, CADTH, and NICE. While AMCP requires "a clear and systematic" process for identifying the inputs used in the economic model, only NICE dictates a full SLR of economic evidence for all economic data to be included.
- NICE requests that similar methodology/rigor be applied to SLRs of economic and clinical data:
  1. Methods should be well documented and reproducible.
  2. Overview of studies considered relevant to decision making in the UK should be included.
  3. Quality assessment is required using an appropriate and validated instrument.
- PBAC specifically states that it prefers economic evaluations based on results from direct randomized trials.
- AMNOG does not require information on economic data, except for pricing.

**Quality assessment**

- NICE requires that the quality of each source of evidence included (including unpublished evidenced) should be appraised. Quality assessments will be validated by NICE during the review.
  1. A list of minimum criteria to be assessed for randomized controlled trials (RCTs) are provided by NICE. Other study types must also be assessed using an appropriate and validated quality assessment instrument.
  2. Consideration should be given to how closely the trials reflect routine clinical practice in the UK.
- PBAC requires that the risk of bias is assessed by authors of the systematic review using a validated tool (eg, Assessing the Methodological Quality of Systematic Reviews or Risk of Bias in Systematic Reviews).
  1. Authors should assess bias, confounding, and impact of chance on the findings presented. The quality of the trials or meta-analyses used should be included in an attachment in Section 2.3 of the submission document assessing the internal validity of trials.

**Table 2. Clinical Data Systematic Literature Search Requirements**

| | Germany (AMNOG) | UK (NICE) | Australia (PBAC) |
|---|---|---|---|
| Databases | ▪ MEDLINE, EMBASE, Cochrane, Clinicaltrials.gov, EU clinical trials register, International Clinical Trials Registry Platform Search Portal, Klinische Prüfungen PharmNet.Bund | ▪ None specified | ▪ (Suggested) MEDLINE, EMBASE, Cochrane Library, ClinicalTrials.gov, International Clinical Trials Registry Platform, Australian Clinical Trials Registry, internal registries |
| Formal Requirements | ▪ Inclusion and exclusion criteria strictly according to German label; study length critical for chronic conditions (≥26 weeks)<br>▪ Validated filter for RCT required; search separated in blocks: intervention, condition,<br>▪ Study methodology 2-step approach: title/abstract screening followed by full text | ▪ The comparators and the relevant patient group(s) are defined in the scope developed by NICE<br>▪ Documentation and rationale should be thorough enough that the methods are reproducible<br>▪ *A priori* protocol and relevant comparators required<br>▪ Each study meeting the criteria for inclusion should be critically appraised<br>▪ Potential treatment effect modifiers should be identified before data analysis, either by a thorough review of the subject area or discussion with experts in the clinical discipline<br>▪ Pairwise or network meta-analysis preferred; narrative assessments will be interpreted with caution<br>▪ If QoL data are not available from the included clinical trials, a separate SLR is required | ▪ Search filters should initially be set to include only randomized trials<br>▪ Search terms and MeSH related to study design, population, intervention, and comparator should be used |
| Documentation | ▪ Search string, name of database, date of search, time horizon of search, # of hits, Cochrane flow chart, documentation of reason for exclusion (for full text screening)<br>▪ Research information systems files must be submitted | ▪ A list of all information sources and the full electronic search strategies for databases, including any limits applied<br>▪ A table describing inclusion and exclusion selection criteria, language restrictions, and the study selection process, with justification as needed to ensure that the rationale for study selection is transparent<br>▪ A flow diagram of the numbers of studies included and excluded at each stage, developed using a validated statement for reporting systematic reviews and meta-analyses<br>▪ A complete reference list of included and excluded studies, and a log with rationale for inclusion or exclusion of each study<br>▪ Having more than 1 reviewer assess all records increases validity; procedure for resolving disagreements should be reported<br>▪ Quality assessment must be conducted for each trial | ▪ Search strategy for identifying nonrandomized studies and studies involving the proposed medicine in other indications<br>▪ Search terms for the literature review (category, description, and search terms), record of search strategies for each database searched (date searched, date span of search, and details of search (the complete MEDLINE search strategy, including search terms, indexing terms, filters, and Boolean operators, should be provided in the submission). For other sources, date searched, date span of search, and any key differences from the complete search strategy provided for the MEDLINE search<br>▪ PRISMA flowchart<br>▪ List of any randomized trials against other comparators that were excluded, and a master list of relevant randomized trials<br>▪ Complete list of trials included for indirect comparisons (and brief reason why they were included) |
| Updates Prior to Submission | ▪ 3 months | ▪ 6 months | ▪ None specified |

Key: AMNOG – Arzneimittelmarkt-Neuordnungsgesetz; MeSH – medical subject headings; NICE – National Institute for Health and Care Excellence; PRISMA – preferred reporting items for systematic reviews and meta-analyses; QoL – quality of life; RCT – randomized controlled trial; SLR – systematic literature review; UK – United Kingdom.

**Table 3. Economic Data Systematic Literature Search Requirements**

| UK (NICE) | | | |
|---|---|---|---|
| Requirements | Required | Scope/objective | Retrieve cost-effectiveness studies relevant to decision making in the UK |
| Databases | Published NICE technology appraisals, the published literature and from unpublished data held by the company | Formal Requirements | Resource use and cost data should be identified systematically |
| Documentation | Methods must be justified and sufficient detail provided so that the search could be reproduced<br>Should provide description and quality assessment of all included studies | Update | None specified |

Key: NICE – National Institute for Health and Care Excellence; UK – United Kingdom.

## CONCLUSIONS

- Frequently, HTA-level SLRs may require additional time for appropriate design and conduct. For example, specific tasks that may be outside of the "norm" for an informal evaluation of the literature require substantial effort and time—such as searching of additional data sources, dual screening of citations, detailed data extraction with full data validation, quality assessment based on specific HTA-recommended checklists, and timely updates of the SLR prior to submission.
- To meet the stringent requirements for conducting an SLR acceptable to many of the major HTA markets, careful consideration must be given to the SLR methodology and to the design of the SLR protocol. Selection of the optimal SLR approach will require not only thoughtful evaluation of the key research questions and topics to be included, but also a close inspection of the methodology needed to align with planned HTA submissions.
- Various key stakeholders such as global and local market access teams should be involved in the design of the SLR. Individuals responsible for conducting cost-effectiveness analyses and mixed treatment comparisons should also be consulted during SLR development.

## REFERENCES

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