BALANCING GLOBAL HTA REQUIREMENTS FOR LITERATURE REVIEWS ACROSS EUROPE, NORTH AMERICA, AND ASIA

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OBJECTIVE:

- To describe and compare systematic literature review (SLR) methodological requirements from health technology assessment (HTA) agencies in different jurisdictions around the world.
- To critically evaluate the quality of SLRs presented in HTA assessments based on the methodological requirements from HTA agencies in different jurisdictions around the world.

TAKE HOME MESSAGE:

- For all reviews, besides comprehensiveness, transparency in the methodology and the minimization of bias is key to the provision of relevant evidence for national HTAs.
- Key differences between HTA agency requirements must be considered when developing an SLR to be used for submissions across global markets.
- SLRs conducted for the purposes of HTA submission generally conformed with the different methodological requirements from HTA agencies in different jurisdictions around the world.

INTRODUCTION

- The requirements from HTA agencies for evidence requirements and the use of methodologies such as SLRs to collect evidence are known to vary.
- SLRs provide comprehensive, high-quality synthesis of published evidence, and are an essential component of submissions for many HTA agencies.
- While there is a pronounced consensus among HTA bodies that an SLR is essential to identify relevant data, specific guidance on data sources, methodology, required outcomes, and reporting of the SLR varies considerably between HTA agencies. In addition, it is not clear to what extent SLRs in HTA submissions conform to the specific requirements dictated by the HTA agencies.

METHODS

- Websites of the most prominent HTA agencies were searched to identify guidance documents detailing SLR requirements. The websites of the following countries/regions were searched: Australia (PBAC), Canada (CADTH), England (NICE), France (HAS), Germany (IQWiG/G-BA), Ireland (NCPE), Scotland (SMC), Sweden (TLV), USA (AMCP, ICER), Thailand (HITAP) and Europe (EUnetHTA).
- Additionally, joint clinical assessments (JCAs) from EUnetHTA were identified for the time period of 2014-2019 for oncology and diabetes products. The corresponding submissions were obtained from the websites of NICE and IQWiG.
- Searches were conducted in May 2019 and an update was done in September 2019. Information from the relevant sources was extracted based on a framework defined a priori following which a descriptive overview of the main findings was prepared and reported.

RESULTS

HTA requirements for SLRs

Type of SLR

- All HTA websites included information regarding the type of literature review required to provide evidence for a product submission. The HTA agencies from the UK required the most types of literature reviews (Table 1).
  - Apart from AMCP and ICER, all other agencies reviewed require an SLR evaluating clinical data and explicitly mention inclusion of comparator data. This is the case with the guidance from EUnetHTA, given that the objective is a clinical assessment.
  - SLRs on economic evidence (economic evaluations, model inputs such as costs and resource use estimates, utilities) are often required by the HTA agencies, but only NICE dictates an SLR of economic evidence (Table 1).

Timing of SLR conduct before submission

- To ensure that the most current clinical data are available for authorities, NICE and IQWiG explicitly request that manufacturers update their SLRs of the clinical data. AMNOG requires the most recent updates before submission (3 months prior to submission) (Table 1).

Methodological guidance

- Overall, HTA guidance documents recommends consulting the Centre for Reviews and Dissemination (CRD) guidelines (2009)[1] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (2009)[2] to conduct SLRs.
- NICE and IQWiG requirements for SLRs are the most prescriptive, whereas the others have few explicit requirements. The recent guidance from EUnetHTA addresses the needs of most European HTA agencies.

Methodological guidance (cont.)

- Methodological requirements are generally less comprehensive for economic reviews than those required for an SLR set out to identify clinical evidence. Key aspects of the review methodology for clinical and economic reviews specified by the different HTA agencies are presented.
  - Sources: For all the reviews, online databases such as Medline, Embase and the Cochrane Library should be searched, and be supplemented with trial registries and conference proceedings. There is no specific guidance on how and what type of information from conference proceedings and trial registries should be consulted. For economic reviews, EconLit and HTA reports should be included as relevant sources.
  - Identification and selection: The use of a search strategy that considers validated filters is specified by several agencies including the guidance from EUnetHTA with the objective to maximize sensitivity and specificity of the search strategy to capture relevant evidence. Defining PICOS prior to the conduct of the SLR is recommended by most HTA agencies (for example, IQWiG requires the PICOS to be in-line with the German label and NICE defines a scope document). SLRs are recommended to be conducted with two reviewers and it is expected that reasons for inclusion and exclusion of evidence is documented and reported by all agencies apart from AMCP and ICER.
  - Quality assessment and critical appraisal: All HTA agencies recommend that the quality of published and unpublished studies should be appraised using an appropriate and validated quality assessment instrument. Recommended tools vary across HTA agencies. For example, a list of minimum criteria to be assessed for randomized controlled trials (RCTs) is provided by NICE. PBAC recommends the use of a validated tool called "Assessing the Methodological Quality of Systematic Reviews or Risk of Bias in Systematic Reviews". For SLRs on economic evidence, the Drummond and Jefferson (1996) checklist[3] for economic evaluations is mandated by the HAS and NICE. Authors of the SLR are required to assess bias and confounding.

Table 1 Submission requirements per HTA agency

✓= required ✗ = not required – = no guidance provided

Submission Requirement		Australia (PBAC)[4]	Canada (CADTH)[5]	England (NICE)[6]	Europe (EUnetHTA)[7]	France (HAS)[8]	Germany (IQWiG)[9]	Ireland (NCPE)[10]	Scotland (SMC)[11]	Sweden (TLV)[12]	Thailand (HITAP)[13]	USA	
												(AMCP)[14]	(ICER)[15]
Type of SLR	SLR of clinical data for the technology and its comparators	✓	✓[a]	✓	✓[b]	✓	✓	✓	✓	✓	✓	✗	✗
	SLR of economic models for technology	✗	✗	✓	✗	✓	✗	✗	✓	-	✗	✓[d]	✗
	SLR of health care resource use and cost	✗	✗	✓	✗	-	✗	✓	✓	✗	✗	✗	✗
	SLR of utility data	✗	✗	✓	✗	✗	✗	✓	✗	✗	✗	✗	✗
Sources, identification and selection of evidence	Published literature & Trial databases	✓	✗	✓	✓	✓	✓	✓	-	-	✓	✗	✗
	Used of search filters	✓	✗	✓	✓	-	✓	-	-	-	✗	✗	✗
	PICOS definition prior to conducting the review	✓	✗	✓	✓	✓	-	✓	✓	-	✗	✗	✗
	Two reviewers	✓	✗	✓	✓	✓	✗[c]	✓	✓	✓	-	✗	✗
	Reasons for inclusion & exclusion	✓	✗	✓	✓	✓	-	-	✓	✓	✓	✗	✗
Quality assessment and critical appraisal	Quality assessment	✓	✗	✓	✓	✓	✗	✓	✓	✓	✓	✗	✗
	Critical appraisal of RCTs and non-RCTs	✓	✗	✓	✓	✓	-	✓	✓	✓	✓	✗	✗
	Critical appraisal of economic models	✗	✗	✓	✗	✓	-	✗	✗	✗	✗	✗	✗

[a] only for new oncology drugs; [b] non-binding recommendations; [c] justification for single reviewer; [d] the process for identifying, evaluating, and selecting all of the data in the model should be clear and systematic

Evaluation of SLR methodology adopted in HTA submissions

- Across all the assessments (NICE, IQWiG and EUnetHTA JCA) included in the evaluation, information on the conduct of the SLR was not available in the NICE assessments. The authors speculate that a SLR may have not been performed in these specific cases due to the availability of evidence from head-to-head clinical trials.
- Consequently an evaluation and comparison of SLR methodology adopted in the EUnetHTA JCAs and IQWiG submissions are presented.
- Overall, the submitted SLR evidence adhered to the recommended sources for both IQWIG and EUnetHTA. The only difference between EUnetHTA SLRs compared to IQWIG SLRs is the inclusion of conference proceedings.
- All searches were conducted 2 months before submission for IQWIG and between 1 to 4 months before submission to the EUnetHTA; these timeframes are in-line with the requirements.
- Details of the search strategy and results are provided per database; screening results were provided with reasons for inclusion/exclusion.
- PICOS criteria were predefined and two reviewers were used for screening, although the latter is not strictly required according to the IQWiG guidance for SLRs.
- Quality assessments and critical appraisals were performed in the SLRs submitted in all EUnetHTA JCAs and IQWiG submissions.

Table 2 SLR submission details across different products for EUnetHTA and IQWIG

✓= required ✗ = not required – = no guidance provided

Agency	Product	Search date (last update) before submission	Published literature databases	Trial databases	Conference proceedings	Search strings provided per database	PICOS pre-definitions	Two reviewers	Reasons for inclusion/Exclusion of studies	QA/critical appraisal performed
Europe - EUnetHTA	Alectinib (NSCLC)[16]	1 month	✓	✓	✓	✓	✓	-	✓	✓[a]
	Midostaurin (AML)[17]	2 months	✓	✓	✓	✓	✓	-	✓	✓
	Regorafenib (HCC)[18]	4 months	✓	✓	✓	✓	✓	✓	✓	✓
	Canagliflozin (Type 2 Diabetes mellitus)[19]	NR	✓	✓	✓	✗	-	-	✗	✓[a]
Germany-IQWiG	Alectinib (NSCLC)[20]	2 months	✓	✓	✗	✓	✓	✓	✓	✓[a]
	Midostaurin (AML)[21]	2 months	✓	✓	✗	✓	✓	✓	✓	✓[a]
	Regorafenib (HCC)[22]	2 months	✓	✓	✗	✗	✓	✓	✓	✓[a]
	Canagliflozin (Type 2 Diabetes mellitus)[23]	2 months	✓	✓	✗	-	✓	✓	✓	✓[a]

[a] Only applies to RCTs

DISCUSSION & CONCLUSIONS

- The most stringent guidelines for SLR methodology were seen in Europe (UK and Germany) and Australia whereas the North American HTAs' guidance for the conduct and documentation of evidence development varied.
- In Europe, EUnetHTA guidelines for SLRs aim to provide a comprehensive clinical assessment that accommodates the needs of all the member states of the European Union (EU). Therefore, specific attention should be given when preparing an SLR for EUnetHTA submission.
- Key differences between HTA agency requirements must be considered when developing an SLR to be used for submissions across global markets.
- Almost all HTA agencies guideline require the inclusion of study registries for SLRs. However, they are vague on the reason for inclusion of study registries and the type of data that would be needed from study registries.
- For all SLRs, besides comprehensiveness, transparency in the methodology and the minimization of bias is key to the provision of relevant evidence for national HTAs.

REFERENCES

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