Evidence Review Group Criticism of Clinical Effectiveness SLRs in NICE Oncology Submissions

Poster HTA137

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Background

- Clinical effectiveness evidence is a key component of pharmaceutical companies' health technology submissions to the UK National Institute for Health and Care Excellence (NICE) and must be sought via systematic literature reviews (SLRs).[1]
- NICE Evidence Review Groups (ERGs) critically appraise submissions from manufacturers on the clinical effectiveness of new technologies, and this has potential implications for decision-making on the inclusion of such technologies in current guidance.

Objectives

To identify where, and better understand why, ERGs have criticised SLRs on clinical effectiveness, we reviewed their responses to recent oncology-related submissions.

Methods

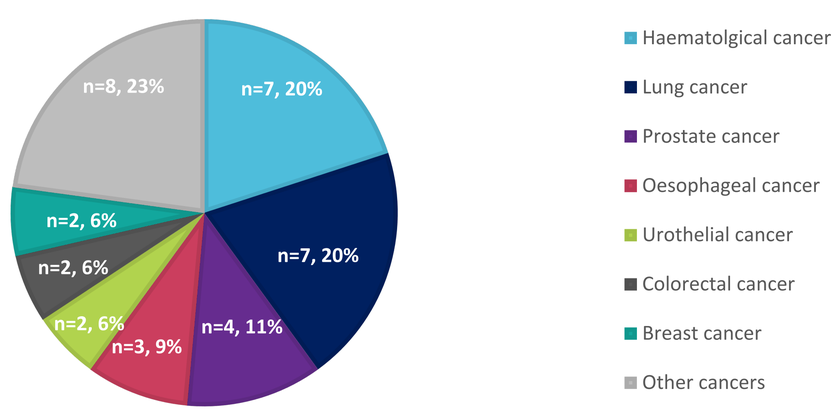
- We searched NICE's website[2] on 14 April 2022 to identify relevant health technology assessments (HTAs), including ERG reports, of oncology drugs published in the previous 12 months.
- The identified HTA documents were screened by a single reviewer to identify ERG criticism of clinical effectiveness SLRs included in the related submissions.
- Details of specific critiques were extracted by a single reviewer using a Microsoft Excel®-based, standardised form, and categorised into the following five pre-defined domains of SLR methodology: *Search methods; Choice/use of selection criteria; Screening methods/results; Data extraction/summarisation;* and *Quality assessment*.
- All critiques initially classified under the pre-defined five domains were further grouped into specific sub-domains, to enable deeper analysis and facilitate better understanding of the criticised areas. Narrative synthesis was conducted to summarise the available data.

Results

HTA Overview

- We identified 35 oncology HTAs, with most of the submissions being related to indications in haematological cancer (20%), lung cancer (20%), or prostate cancer (11%) (**Figure 1**).
- Most of the HTAs had resulted in positive recommendations from NICE (91%).

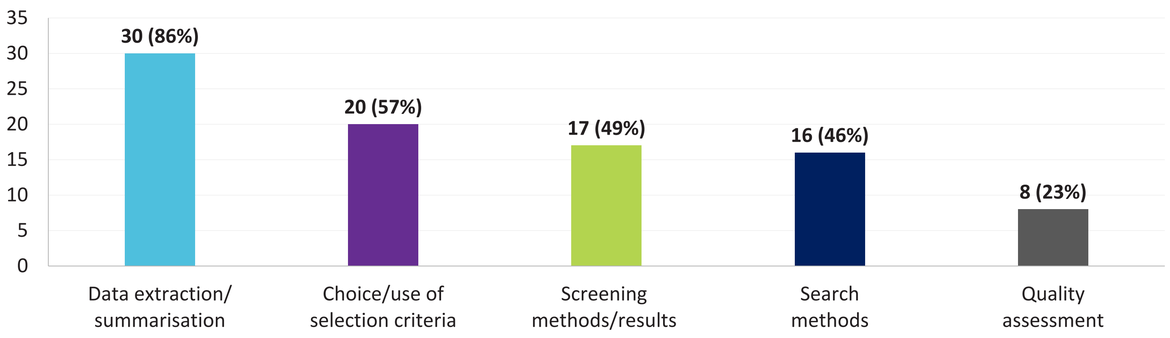
Figure 1. Oncology indications in included NICE HTAs (number of HTAs, %)



Critiques Overview

- Across the 35 reviewed oncology HTAs, we identified 133 unique criticisms in total, a mean of 3.8 criticisms per HTA submission. All but two HTAs included at least one criticism of the clinical effectiveness SLR.[3,4]
- Submissions were most commonly criticised for limitations in the *Data extraction/summarisation* domain (in 86% of HTAs), and least often criticised for limitations in the *Quality assessment* domain (23%) (**Figure 2**).

Figure 2. Distribution of criticised domains in oncology HTA submissions (number of HTAs, %)



Results (cont'd)

- Across all the sub-domains, the specific concerns most frequently raised by ERGs were related to incomplete data extraction (in 86% of HTAs), followed by missing or inappropriate comparator(s) (43%), and unclear search methods (34%) (**Table 1**). Inadequate documentation of various aspects of the SLR methodology used was a common theme among the sub-domain criticisms noted by the ERGs.
- Sub-domain limitations that were least often cited by the ERGs (i.e., in only a single HTA each) included the use of redundant search syntax; instances of missing selection criteria; the inclusion of irrelevant studies; and inadequacy of the chosen quality-assessment methodology.
- Among HTAs with criticisms in the *Search methods* domain, besides unclear search methods (in 75% of the HTAs represented in the domain), common limitations cited included the use of inappropriate search filters (50%), and the absence of documented search strategies (31%).
- With regards to the criticisms of the *Choice/use of selection criteria* domain, the HTAs involved most often included criticism for missing or inappropriate comparator(s) (75%), with the next most commonly cited limitations being the consideration of a population not aligned with the decision problem (35%), and exclusion of relevant studies (10%).
- In the *Screening methods/results domain*, the ERG groups most often cited inadequate documentation of study attrition (47%) and of screening methods (47%).
- In all of the HTAs represented in the *Data extraction/summarisation* domain, there were some specific criticisms of incomplete data extraction, while comparatively few of these HTAs included criticism citing inaccurate extraction of study data (17%).
- Finally, the ERG concerns related to the Quality assessment domain were most often due to inadequate documentation of the methods used to conduct such assessments (in 50%), followed by incorrect quality-assessment decisions (25%), and missing quality assessment (25%).

Table 1. Specific ERG criticisms in included oncology HTAs

DOMAINS	SUB-DOMAINS			
Domain Type	**Sub-domain Types**	**HTAs with sub-domain type criticism (n)***	**As % of all identified HTAs†**	**As % of the HTAs represented in the domain¥**
Search methods (HTAs with domain-type criticism, n=16) [5-20]	Unclear search methods	12	34	75
	Inappropriate search filters	8	23	50
	Missing search strategies	5	14	31
	Missing data sources	4	11	25
	Missing/misused search terms	4	11	25
	Questionable search limits	4	11	25
	Outdated searches	3	9	19
	Redundant search syntax	1	3	6
Choice/use of selection criteria (n=20) [5-7,9-13,17,19,21-28]	Missing/inappropriate comparator(s)	15	43	75
	Population not in line with the decision problem	7	20	35
	Relevant studies wrongly excluded	2	6	10
	Missing study selection criterion	1	3	5
	Irrelevant studies included	1	3	5
Screening methods/ results (n=17) [5-7,9-18,20-24,26-37]	Inadequately documented study attrition	8	23	47
	Inadequate documentation of methods	8	23	47
	Published articles not provided to ERG	2	6	12
Data extraction/ summarisation (n=30) [5-7,9-18,20-24,26-37]	Incomplete extractions	30	86	100
	Inaccurate data extraction	5	14	17
	No information on extraction methods	4	11	13
Quality assessment (n=8) [6,9,12,14,19,22,23,31]	Inadequate documentation of methods	4	11	50
	Inadequate assessment of studies quality	2	6	25
	Missing quality assessment	2	6	25
	Inadequate methodology	1	3	13

ERG= Evidence Review Groups; HTA= Health Technology Assessment
*The number of HTAs with at least one critique in a particular sub-domain.
†The denominator is the total number of HTAs identified (n=35).
¥The denominator is the number of HTAs with at least one criticism in the specific domain.

Conclusions

- Evidence suggests NICE ERGs frequently criticise the methodology and documentation of clinical effectiveness SLRs included in company submissions.
- Importantly, most of these limitations appear avoidable, assuming sufficiently rigorous methodology is used to conduct the research.
- Understanding such criticisms may help ensure scientific rigour and transparency in conducting and reporting such SLRs, thereby reducing the need to explain, justify or revise the research to address queries in ERG clarification letters.

References

1. National Institute for Health and Care Excellence. Health technology evaluations: The manual. NICE. https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741. Published 31 Jan 2022 Accessed 1 September 2022.
2. National Institute for Health and Care Excellence. https://www.nice.org.uk/. Published 2022. Accessed 14 April 2022.
3. Nivolumab with ipilimumab for untreated advanced renal cell carcinoma (TA780).
4. Avelumab for untreated metastatic Merkel cell carcinoma (TA691).
5. Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (TA783).
6. Sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (TA781).
7. Pembrolizumab for treating relapsed or refractory classical Hodgkin lymphoma after stem cell transplant or at least 2 previous therapies (TA772).
8. Pembrolizumab with carboplatin and paclitaxel for untreated squamous non-small-cell lung cancer (TA770).
9. Daratumumab in combination for untreated multiple myeloma when a stem cell transplant is suitable (TA763).
10. Nivolumab for adjuvant treatment of resected oesophageal or gastro-oesophageal junction cancer (TA746).
11. Selpercatinib for treating advanced thyroid cancer with RET alterations (TA742).
12. Atezolizumab for untreated PD-L1-positive advanced urothelial cancer when cisplatin is unsuitable (TA739).
13. Pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy for untreated advanced oesophageal and gastro-oesophageal junction cancer (TA737).
14. Nivolumab with ipilimumab and chemotherapy for untreated metastatic non-small-cell lung cancer (TA724).
15. Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 fusion or rearrangement (TA722).
16. Abiraterone for treating newly diagnosed high-risk hormone-sensitive metastatic prostate cancer (TA721).
17. Nivolumab for previously treated unresectable advanced or recurrent oesophageal cancer (TA707).
18. Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies (TA704).
19. Acalabrutinib for treating chronic lymphocytic leukaemia (TA689).
20. Venetoclax with azacitidine for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable (TA765).
21. Apalutamide with androgen deprivation therapy for treating hormone-sensitive metastatic prostate cancer (TA741).
22. Carfilzomib with dexamethasone and lenalidomide for previously treated multiple myeloma (TA695).
23. Chlormethine gel for treating mycosis fungoides-type cutaneous T-cell lymphoma (TA720).
24. Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency (TA779).
25. Nivolumab for advanced non-squamous non-small-cell lung cancer after chemotherapy TA713
26. Nivolumab with ipilimumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency (TA716).
27. Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection (TA761).
28. Selpercatinib for previously treated RET fusion-positive advanced non-small-cell lung cancer (TA760).
29. Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy (TA725).
30. Apalutamide with androgen deprivation therapy for treating high-risk hormone-relapsed non-metastatic prostate cancer (TA740).
31. Atezolizumab monotherapy for untreated advanced non-small-cell lung cancer (TA705).
32. Enzalutamide for treating hormone-sensitive metastatic prostate cancer (TA712).
33. Nivolumab for treating recurrent or metastatic squamous cell carcinoma of the head and neck after platinum-based chemotherapy (TA736).
34. Olaparib plus bevacizumab for maintenance treatment of advanced ovarian, fallopian tube or primary peritoneal cancer (TA693).
35. Pembrolizumab for adjuvant treatment of completely resected stage 3 melanoma (TA766).
36. Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy (TA692).
37. Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency (TA709).

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