Review

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Increasing transparency in indirect treatment comparisons: is selecting effect modifiers the missing part of the puzzle? A review of methodological approaches and critical considerations

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Failure to adjust for effect modifiers (EMs) in indirect treatment comparisons (ITCs) can produce biased and uncertain effect estimates. This is particularly important for health technology assessments (HTAs), where the availability of new treatments is based on comparative effectiveness results. Much emphasis has been placed on advancing ITC methods to adjust for EMs, yet whether EMs are appropriately identified for the conduct of ITCs in the first place is unclear. To understand the extent of guidance and requirements for the selection of EMs for ITCs currently available and if and how this guidance is applied in practice, a series of pragmatic reviews of guidance documents from HTA and non-payer organizations, primary published ITC analyses, and prior HTA submissions in two indications (non-small cell lung cancer and psoriasis) was conducted. The reviews showed that current ITC guidance mainly focused on developing analytical methods to adjust for EMs. Some organizations, such as HTA bodies in the UK, France and Germany, recommended the use of literature reviews, expert opinion and statistical methods to identify EMs. No detailed guidance on the selection process or the appropriate literature review approach was found. Similar trends were identified through the database search and review of prior HTA submissions; only few published ITCs and submissions included information on the EM selection process which was either based on findings from the literature, trial subgroup analyses, or clinical input. No reference to a systematic selection approach was found.

There is an urgent need to fill the guidance gap identified across the reviews by including a step in ITC guidelines on how EMs should be identified through systematic reviews, formal expert elicitation, and a quantitative assessment of the EM distribution. Researchers and manufacturers are also encouraged to improve transparent reporting and justification of their selection of EMs to allow for an independent review of the set of factors being considered for adjustment. Both will contribute toward reducing bias in the ITC results and ultimately increase confidence in decision-making.

Plain language summary: Certain variables that can affect the outcomes of new therapies must be accounted for to avoid bias when comparing the effectiveness of new and existing treatments. This is especially important in indirect treatment comparisons that are included in submissions to agencies which recommend whether a medicine should be financed through the local healthcare system. Previous research has focused on how to adjust for these variables to create an unbiased evaluation, but little information exists on how to appropriately identify them in the first place. A review of guidance documents from reimbursement bodies and other relevant publications demonstrated that there was no detailed guidance on the selection process or a systematic approach to handle this issue. These findings highlight an urgent need to develop guidance that will reduce bias in indirect treatment comparisons and increase confidence in the evidence needed to make new therapies available to the public.

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Tweetable abstract: The lack of guidance on how to identify effect modifiers (EM) for indirect treatment comparisons (ITC) in health technology assessments (HTA) led to a considerable underreporting of the EM selection process in published ITCs and HTA submissions. Further HTA guidance is needed.

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Keywords: comparative effectiveness • effect modifier • health technology assessment • indirect treatment comparison • literature review • matching-adjusted indirect comparison • network meta-analysis • prognostic variable • simulated treatment comparison

Producing unbiased comparative treatment effect estimates on the clinical performance of health technologies under assessment is the cornerstone of healthcare decision-making. The reimbursement assessment of a new technology is based on the appraisal of its value in terms of improving clinical (and cost-) effectiveness outcomes in comparison with other relevant treatments currently used in clinical practice.

When the clinical evidence base for a new health technology is obtained from randomized clinical trials, the direct comparisons to all available treatments reflecting clinical practice and thus relevant to the health technology assessment (HTA) decision problem are rarely available. Therefore, indirect treatment comparisons (ITCs) such as network meta-analyses (NMAs) and population-adjusted indirect comparison (PAIC) methods have been developed to establish the relative clinical effectiveness of new technologies using aggregated or individual patient data, respectively [1,2].

Central to the planning and execution of ITCs based on aggregated trial data is a deliberation whether effect-modifying variables (EMs) differ between studies. EMs (also known as predictive variables) are covariates that can alter the effect of treatment as measured on a given scale [2,3]. EMs are distinguished from prognostic variables (PV) although the terms are sometimes incorrectly used interchangeably [2,4]. For clarity, PVs are covariates that affect the outcome, irrespective of treatment, and therefore do not interfere with the relative treatment effect estimates as calculated in ITCs. Any evidence of effect modification or absence of trial data on known EMs may lead to biased or uncertain results in comparative treatment effects that can ultimately affect the confidence in decision-making [5,6]. Likewise, adjusting for factors that are not actually EMs for a specific outcome can unnecessarily increase uncertainty [2,7]. This is because the loss of effective sample size due to (over) adjustment for additional factors inherently reduces the precision around the results [8,9].

Against that background, it is important to employ a robust approach for identifying whether and which EMs are critical for inclusion in ITCs given their weight in the validity of analyses results. This review aimed to identify and categorize the methodological approaches of identifying EMs in ITCs both from an HTA requirement standpoint and their use in practice, by summarizing related evidence from three sources: existing guidance by HTA bodies and other organizations, primary research from published literature and HTA submissions in two specific disease areas.

Methods

A series of comprehensive (pragmatic) reviews was conducted to determine what guidance is available for the appropriate identification and selection of EMs when conducting ITCs and how this guidance has been applied in practice; the review included guidance documents from HTA bodies and non-payer organizations, published ITCs and prior HTA submissions in key representative indications. The review focused on how EMs are identified and was not intended to summarize the methodologies used to adjust for EMs. The reviews were restricted to articles in English; however, no geographic restrictions were otherwise applied. The searches of published ITCs and HTA submission documents were also restricted to those published since 2015 and 2017, respectively. This is because one of the key guidance documents in this area – the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) Document 18 – was first published in December 2016, highlighting the relatively recent focus on more advanced methods to adjust for EMs in the context of ITCs [2].

Searches were first conducted in November 2021 and updated in February 2023 across HTA bodies, non-payer organizations and literature databases (Embase and MEDLINE via Ovid SP; Supplementary Table 1) to describe the requirements for the selection of EMs for ITCs and how this was applied in ITCs subsequently published in peer-reviewed journals. Articles on NMA/ITCs identified through the database searches that did not explicitly refer to these concepts in title or abstract were not selected further. Conference abstracts, letters, editorials, or

narrative reviews were excluded. Furthermore, pairwise meta-analyses or publications on statistical methods for the adjustment of EMs were not considered. Overview of reviews (also called umbrella reviews) were not considered as they typically do not provide the breadth of information to allow elaboration of issues around EM selection and we considered that any relevant primary ITCs would have already been identified by the literature searches.

The websites of NICE and the Canadian Agency for Drugs and Technologies in Health (CADTH) were reviewed for submissions in non-small cell lung cancer (NSCLC) and psoriasis – an oncology indication and a chronic disease with rapidly changing treatment landscapes – as example case studies to identify how EMs and PVs (given that these terms are frequently used interchangeably) were identified and selected in the context of ITCs for the reimbursement of pharmaceuticals. The search was restricted to NICE and CADTH as other HTA bodies usually only publish submission summaries, which did not provide sufficient information for the purpose of the current review (Supplementary Table 2). Only the latest version of each submission or re-submission was included. Terminated appraisals were not considered.

The reviews were supplemented by Google searches and a snowballing approach using the identified articles. Information on the search strategies is provided in the online appendix.

All screening was conducted by one researcher, with a second, more senior researcher conducting quality assurance checks. The final list of records informing this publication was agreed through discussions among the researchers. Information from the relevant documents was extracted into pre-defined data extraction sheets specifically designed for each review type. All extractions were validated by a second researcher.

Themes across these publications were summarized qualitatively with the aim to identify relevant topics in individual documents and provide a critical assessment of proposed selection approaches for EMs in the context of ITCs for healthcare decision-making.

Results

Guidance documents from HTA bodies & non-payer organizations

The searches identified 15 relevant guidance documents and methods manuals across six HTA bodies (NICE, CADTH, Institute for Quality and Efficiency in HealthCare [IQWiG]/Federal Joint Committee [G-BA], Haute Autorité de Santé [HAS], Pharmaceutical Benefits Advisory Committee [PBAC], and the Institute for Clinical and Economic Review [ICER]) and three non-payer organizations that referred to the role of EMs and their potential impact on the validity of ITC analysis results. Six documents (one each from the NICE DSU [10], IQWiG [11], CADTH, The Professional Society for Health Economics and Outcomes Research [ISPOR] [12], Cochrane [13] and ICER [14]) focused on statistical methods to address EMs when conducting ITCs but did not provide guidance on how these variables should be systematically and comprehensively identified. The remaining nine documents (six were published by four different HTA agencies including NICE [2,15,16], G-BA [17], HAS [18], and PBAC [19], and three were from the non-payer organizations ISPOR [20] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses group [21,22]) provided some guidance on the topic of EM selection. A full description of individual documents is presented in Table 1.

Across the HTA guidance documents, two main themes were identified regarding the identification of EMs for ITCs (Figure 1).

- EMs should be identified before conducting the ITC data analysis through targeted literature reviews or using expert opinion (three of the HTA guidance documents were published by NICE [16] and the NICE DSU [2,15], plus one each from HAS [18], PBAC [19] and the G-BA [17]).
- An assessment is needed whether pre-selected factors are acting as EMs in specific ITC scenarios using quantitative methods such as homogeneity or interaction tests (G-BA [17] and HAS [18]), subgroup analyses of relevant clinical trials (HAS [18] and NICE [2]), or quantitative or qualitative assessments of the transitivity assumption, that is, there are no considerable differences in the distribution of EMs across trials (PBAC [19]).

From non-HTA bodies, guidance was restricted to adequate reporting of EM selection. However, it was outside the scope of these checklists to provide specific guidance on the EM selection method [20–22].

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Table 1. Guidance Document Review – Key Findings.

Organization	Title of guidance document	Year of publication	Specific guidance on how to identify EM?	Key findings	Ref.
HTA body					
NICE DSU	TSD 18: Methods for population-adjusted indirect comparisons in submissions to NICE	2016	Yes	Reference to the manual of health technology evaluations, which states that a thorough review of the subject area or discussion with clinical experts is needed.	[2]
NICE DSU	TSD 7: Evidence synthesis of treatment efficacy in decision making: a reviewer's checklist	2012	Yes	Checklist for evidence synthesis of treatment efficacy (question on whether EMs were identified through a literature review, and whether differences in patient populations were accounted for).	[15]
NICE DSU	TSD 3: Heterogeneity: subgroups, meta-regression, bias and bias-adjustment	2012	No (guidance on how to address the presence of EMs)	Guidance focuses on the adjustment for EMs. No information on how EMs should be identified or selected.	[10]
NICE	NICE health technology evaluations: the manual	2022	Yes	Potential EMs should be identified before data analysis through a review of the subject area or discussion with experts in the clinical discipline.	[16]
G-BA	Dossier zur Nutzenbewertung gemäß § 35a SGB V (dossier for benefit assessment)	2019	Yes	Potential EMs should be investigated through homogeneity or interaction tests based on regression analyses. Subgroup analyses using IPD are preferred. If clinically plausible, the following factors should be investigated: sex, age, disease severity or stage, geography, single- vs multi-centre studies. All a priori-defined subgroup analyses should also be considered. No further information on how EMs should be selected.	[17]
HAS	Indirect comparisons methods and validity	2009	Yes	Interaction covariables should be identified through subgroup analyses conducted in the relevant clinical trials and interaction tests.	[18]
PBAC	Guidelines for preparing a submission to the Pharmaceutical Benefits Advisory Committee (v5)	2016	Yes	Differences in factors violating the transitivity assumption should be investigated qualitatively and quantitatively. No guidance on how these factors should be (systematically) identified.	[19]
ICER	2020–2023 Value Assessment Framework	2020	No (guidance on how to address the presence of EMs)	The document states that in some cases, factors are known to account for EMs. The framework also states that ICER will consider EMs in the discussion. No formal guidance on how EMs should be identified is given.	[14]
IQWiG	General methods (v6.1)	2022	No (guidance on how to address the presence of EMs)	No guidance on how EMs should be systematically identified. Guidance given on how subgroup analyses should be conducted, especially in the presence of multiple EMs.	[11]
CADTH	Procedures for CADTH Reimbursement Reviews [Sponsor Summary of Clinical Evidence Template]	2023	No (only top-level guidance available)	Potential EMs should be identified before data analysis. No clear guidance on how EMs should be identified.	[45]
Non-payer organizations					
ISPOR Task Force	Interpreting Indirect Treatment Comparisons and Network Meta-Analysis for HealthCare Decision Making: Report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: Part 1	2011	Yes	Simplified checklist to assist decision-makers in evaluating a reported NMA. The NMA publication should include a table or list of studies with information regarding study design and patient characteristics that might act as EMs.	[20]
ISPOR Task Force	Conducting Indirect-Treatment-Comparison and Network-Meta-Analysis Studies: Report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: Part 2	2011	No (guidance on how to address the presence of EMs)	No guidance on how EMs should be identified.	[12]
PRISMA group	Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data: The PRISMA-IPD Statement	2015	Yes	Checklist for SLRs and MAs of IPD that includes an item on the identification of potential EMs.	[22]

CADTH: Canadian Agency for Drugs and Technologies in Health; DSU: Decision Support Unit; EM: Effect modifier; G-BA: Gemeinsamer Bundesausschuss (Federal Joint Committee); HAS: Haute Autorité de Santé; HTA: Health technology assessment; ICER: Institute for Clinical and Economic Review; IPD: Individual patient data; IQWiG: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in HealthCare); ISPOR: The Professional Society for Health Economics and Outcomes Research; MA: Meta-analysis; NICE: National Institute for Health and Care Excellence; NMA: Network meta-analysis; PBAC: Pharmaceutical Benefits Advisory Committee; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SGB: Sozialgesetzbuch (social code); SLR: Systematic literature review; TSD: Technical support document.

Table 1. Guidance Document Review – Key Findings (cont.).

Organization	Title of guidance document	Year of publication	Specific guidance on how to identify EM?	Key findings	Ref.
PRISMA group	The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of HealthCare Interventions: Checklist and Explanations	2015	Yes	Guidance document on how NMAs should be reported. Recommendations across various items to report collected data on EMs (including from additional sources). No clear guidance on how EMs should be identified.	[21]
Cochrane group	Cochrane Handbook for Systematic Reviews of Interventions	2022 (access date)	No (guidance on how to address the presence of EMs)	Characteristics used for subgroup analyses or meta-regression should be pre-specified in the protocol. No clear guidance on how EMs should be identified.	[13]

CADTH: Canadian Agency for Drugs and Technologies in Health; DSU: Decision Support Unit; EM: Effect modifier; G-BA: Gemeinsamer Bundesausschuss (Federal Joint Committee); HAS: Haute Autorité de Santé; HTA: Health technology assessment; ICER: Institute for Clinical and Economic Review; IPD: Individual patient data; IQWiG: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in HealthCare); ISPOR: The Professional Society for Health Economics and Outcomes Research; MA: Meta-analysis; NICE: National Institute for Health and Care Excellence; NMA: Network meta-analysis; PBAC: Pharmaceutical Benefits Advisory Committee; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SGB: Sozialgesetzbuch (social code); SLR: Systematic literature review; TSD: Technical support document.

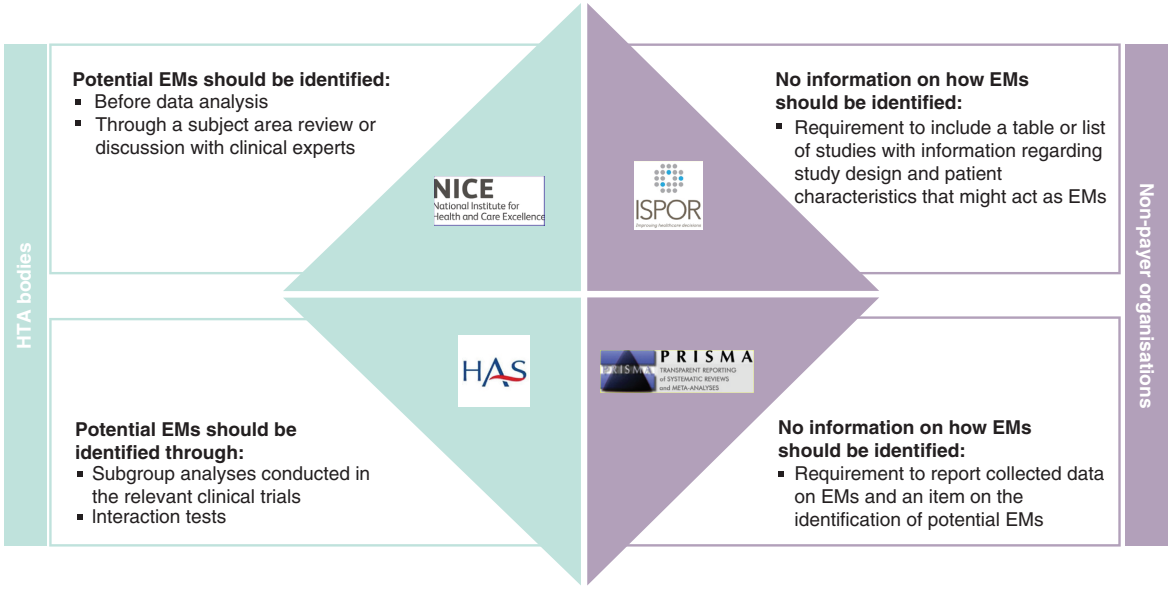

Figure 1. Summary of themes identified in payer and non-payer guidance documents.
EM: Effect modifier; HTA: Health technology assessment.

Application of guidance in the literature & prior HTA submissions

Pragmatic review of ITCs published in peer-reviewed journals

Of the 511 unique articles identified through the Embase and MEDLINE search, 17 mentioned a selection process for interfering variables, such as EMs and PVs (Figure 2 and Supplementary Table 3). Eleven publications reported on ITCs across specific clinical indications [23–33]. Two publications concerned reviews of ITCs irrespective of the indication: a review of population-adjusted analyses across published NICE submissions [7] and a review of previously published NMAs to assess the level of EM reporting [34]. The remaining four publications were protocols of NMAs in Type 1 diabetes [35] and depressive disorder [36–38].

Of the 17 publications, six were on traditional NMAs [24,25,30,31,33,38], three on NMAs using individual patient data (IPD) [35–37], one each on a matching-adjusted indirect comparison (MAIC) [23] and both an NMA and simulated treatment comparison [32], and six publications concerned reviews of NMAs and other forms of ITCs [7,26–29,34].

Only few published ITCs included information on the selection process for EMs which was either based on evidence previously highlighted in the literature, input from clinical experts or findings from prior trial subgroup analyses. No reference to a systematic identification of EMs through literature reviews was found (Figure 3).

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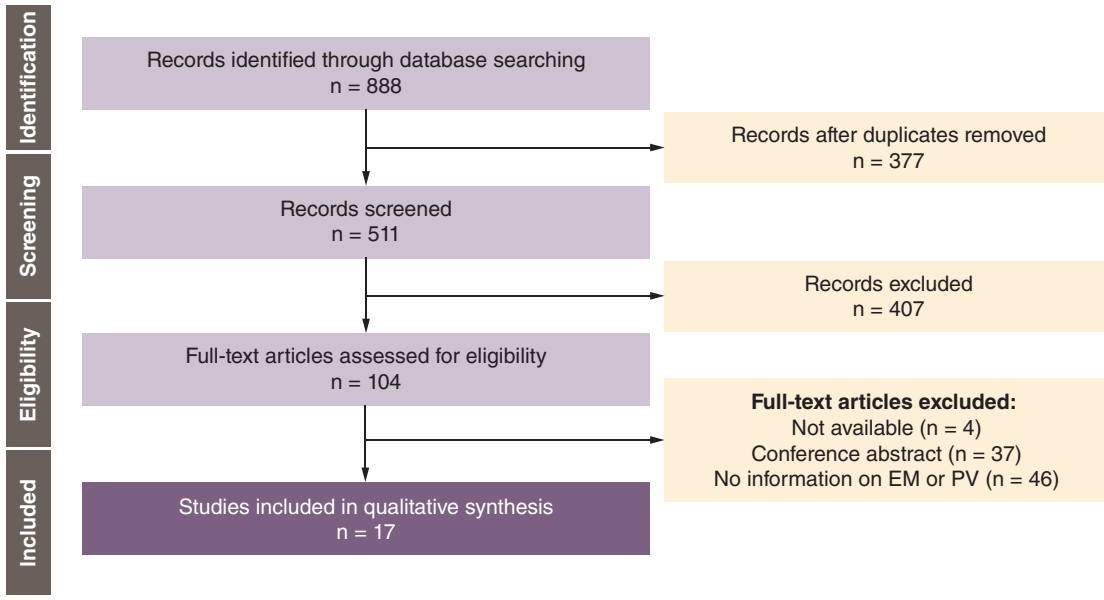

Figure 2. PRISMA flow chart for the review of published indirect treatment comparisons.
EM: Effect modifier; PV: Prognostic variable.

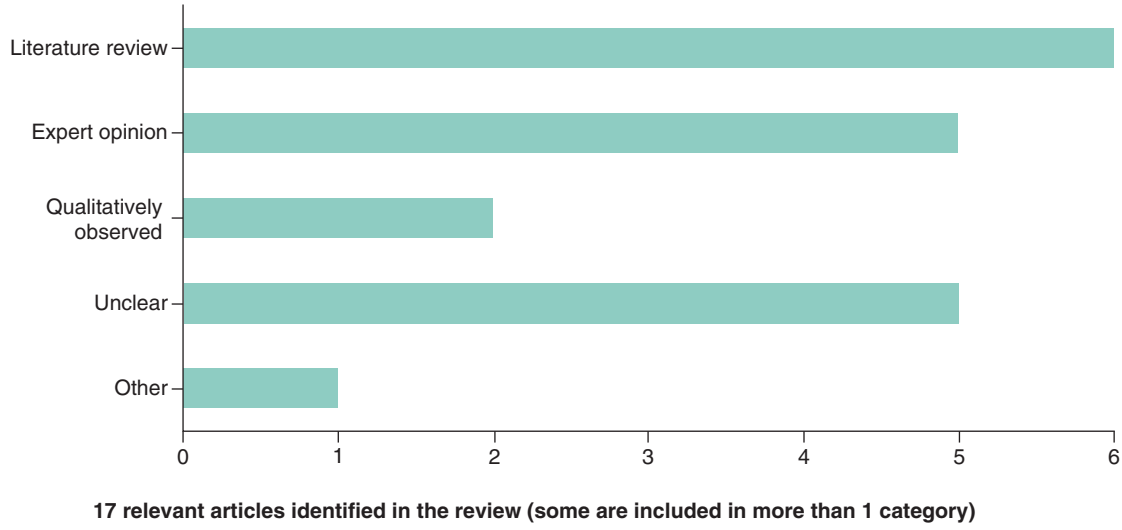

Figure 3. Number of published indirect treatment comparisons by source of effect modifier identification.

Two protocols for an IPD-NMA [36,37] of various interventions for depressive disorder included a list of EMs based on the literature, with both protocols citing the same previously published literature review. Factors to be investigated included age, sex, socioeconomic status, disease history, current symptoms and study characteristics. However, the protocols did not describe whether these factors had been identified through a systematic literature search of EMs. The protocols further stated that the final list of EMs would ultimately depend on the availability of these factors in the identified trials. Similarly, four published NMAs [30–33] provided a list of potential EMs based on information derived from the literature. However, no further information on the literature review approach was provided.

In five articles (two published NMAs [30,32] and three reviews of NMAs and ITCs [7,27,29]), the selection of EMs was based on expert opinion. No further details were provided on whether the discussion with subject matter experts was based on a formal elicitation exercise to justify their inclusion.

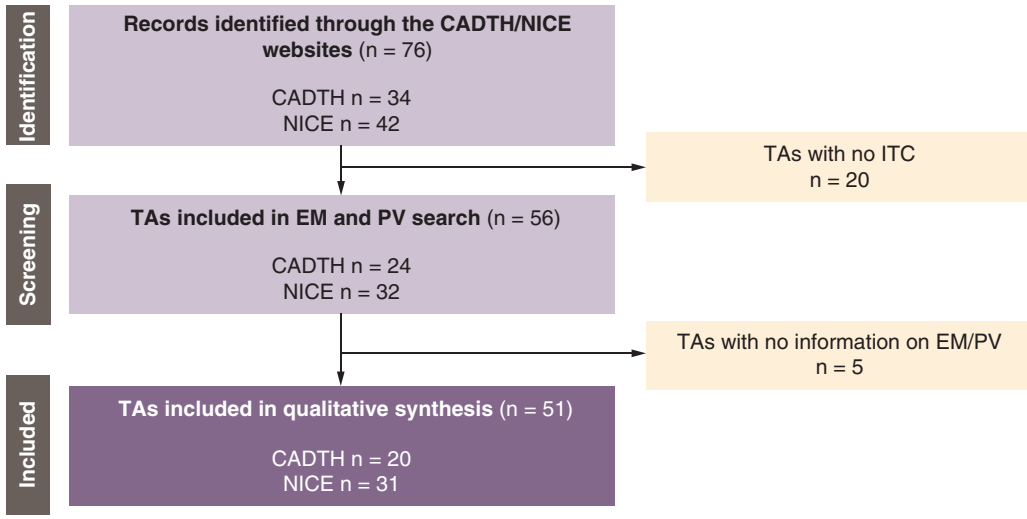

Figure 4. PRISMA flow chart for the review of published Canadian Agency for Drugs and Technologies in Health and national Institute for Health and Care Excellence technology assessments.
CADTH: Canadian Agency for Drugs and Technologies in Health; EM: Effect modifier; ITC: Indirect treatment comparison; NICE: National Institute for Health and Care Excellence; PV: Prognostic variable; TA: Technology appraisal.

Two systematic literature reviews (SLRs) of NMAs [26,34] highlighted issues frequently encountered in the selection of EMs in the context of NMAs/ITCs. In these cases, EMs were mainly identified qualitatively through a comparison of patient baseline characteristics or subgroup results across the trials included in the analyses.

One publication mentioned the application of IPD analyses to identify EMs [35], and the remaining five publications did not provide a clear description of how EMs had been identified [23–25,28,38].

Most publications did not specifically state the timing of EM identification, i.e., whether this exercise was done prior, during or after conducting the analysis. In four cases, EMs were identified at the protocol or statistical analysis plan stage [31,35–37]. For a further nine publications, it was assumed that EMs had been identified prior to conducting the analysis given descriptions of the selection process in the methods. One review of published NMAs reported that of the 11 included studies, seven identified EMs before the conduct of the ITC, one after assessing inconsistency in the network, and three before and after [26]. The remaining three publications did not provide sufficient information on the timing of the EM selection processes [27,28,34].

Pragmatic review of prior HTA submissions

The review identified 51 relevant submissions with an ITC and information on EM/PVs, including 28 standard NMAs, three fractional-polynomial NMAs, five Bucher ITCs, 14 MAICs, and six propensity score weighting analyses, with some submissions including more than one analysis type (Figure 4).

The review of prior CADTH and NICE submissions of treatments for NSCLC (Table 2) and psoriasis (Table 3) confirmed the direction of the trend identified by the review of peer-reviewed, published ITCs in that detailed information on the identification and section of EMs and PVs was rarely available.

Across the manufacturer submissions, specific patient characteristics (e.g., genetic mutations or exposure to prior treatment) of the target populations were most commonly cited as factors that might impact treatment effects or clinical outcomes. In many instances, between-group differences were highlighted with regard to the validity of ITC results, suggesting that differences in patient baseline characteristics were investigated as part of the feasibility assessment. However, no clear information was presented as to whether the differences in baseline characteristics accounted for EMs or PVs. In some cases, the manufacturer submissions also referred to prior submissions as a source for potential EMs.

In CADTH submissions, observed between-group differences in patient characteristics were the most common source of justifying the selection of potential EM/PVs, followed by published evidence and subgroup analyses of the included trials. In contrast, manufacturer submissions to NICE most commonly mentioned clinical advice and information retrieved from the literature as sources for potential EMs and PVs. Only one company submissions (technology appraisal [TA]850 [39] on amivantamab as second- or later-line treatment for NSCLC) specifically

Table 2. Health Technology Assessment Review – Non-small Cell Lung Cancer.

Submission ID	Date of Guidance	Intervention (LoT)	Type of ITC	EM Identification	PV Identification	Timing of EM/PV Identification	Ref.
NICE							
TA428	11 January 2017	Pembrolizumab (2L+)	NMA	–	Based on subgroup analysis	Timing of EM/PV identification is unclear; but likely to have occurred prior to the conduct of the NMA given the focus on trial subgroup analyses	[46]
TA500	24 January 2018	Ceritinib (1L)	MAIC	No information on selection process provided	Based on literature	Timing of EM/PV identification is unclear	[47]
TA520	16 May 2018	Atezolizumab (2L+)	NMA	–	The consistency of overall survival results was examined across subgroups based on important prognostic characteristic (no information on how these were selected)	Timing of EM/PV identification is unclear; but likely to have occurred prior to the conduct of the NMA given the focus on trial subgroup analyses	[48]
TA571	20 March 2019	Brigatinib (2L+)	MAIC	Based on clinical advice	Based on clinical advice	Timing of EM/PV identification is unclear; but likely to have occurred prior to the conduct of the MAIC given the focus on expert elicitation exercises	[49]
TA584	5 June 2019	Atezolizumab (1L)	NMA	–	• Based on literature and clinical advice • Additional PVs identified by ERG	Timing of EM/PV identification is unclear; but likely to have occurred prior to the conduct of the NMA given the focus on expert elicitation exercises to identify factors for the NMA; additional PVs identified by the ERG after the conduct of the original NMA	[50]
TA595	14 August 2019	Dacomitinib (1L)	FP-NMA	Based on literature and clinical advice	–	Timing of EM/PV identification is unclear; but likely to have occurred prior to the conduct of the NMA given the focus on expert elicitation exercises and literature reviews	[51]
TA628	13 May 2020	Lorlatinib (2L+)	MAIC	Based on literature, clinical advice and trial IPD analysis	–	Timing of EM/PV identification is unclear; but likely to have occurred prior to the conduct of the MAIC given the focus on expert elicitation exercises, literature review and analysis of trial IPD	[52]
TA643	12 August 2020	Entrectinib (1L+)	MAIC	• Based on clinical advice • ERG suggested additional EMs following the clinical advice	–	Timing of EM/PV identification is unclear; but likely to have occurred prior to the conduct of the MAIC given the focus on expert elicitation exercises to identify factors for the MAIC; additional PVs identified by the ERG after the conduct of the original MAIC	[53]
TA653	14 October 2020	Osimertinib (2L)	MAIC	–	• Based on literature • ERG suggested additional EMs following the clinical advice	Timing of EM/PV identification is unclear; but likely to have occurred prior to the conduct of the MAIC given the focus on literature reviews to identify factors for the MAIC; additional PVs identified by the ERG after the conduct of the original MAIC	[54]

1L: First line; 2L+: Second line or later; CADTH: Canadian Agency for Drugs and Technologies in Health; EM: Effect modifier; ERG: Evidence review group; FP: Fractional polynomial; ID: Identification; IPD: Individual patient data; ITC: Indirect treatment comparison; LoT: Line of treatment; MAIC: Matching-adjusted indirect comparison; NICE: National Institute for Health and Care Excellence; NMA: Network meta-analysis; NSCLC: Non-small cell lung cancer; pERC: Pan-Canadian Oncology Drug Review Expert Review Committee; PSWA: Propensity score weighting analysis; PV: Prognostic variable; TA: Technology appraisal.

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Table 2. Health Technology Assessment Review – Non-small Cell Lung Cancer (cont.).

Submission ID	Date of Guidance	Intervention (LoT)	Type of ITC	EM Identification	PV Identification	Timing of EM/PV Identification	Ref.
TA654	12 October 2020	Osimertinib (1L)	Bucher ITC	–	–	No information on EM/PV given	[55]
TA670	27 January 2021	Brigatinib (1L)	MAIC	No information on selection process provided	No information on selection process provided	Insufficient information provided to conclude on the timing of identification	[56]
TA683	10 March 2021	Pembrolizumab (1L)	NMA; Bucher ITC	No information on selection process provided	–	Insufficient information provided to conclude on the timing of identification	[57]
TA705	2 June 2021	Atezolizumab (1L)	NMA; FP-NMA	–	No information on selection process provided	Insufficient information provided to conclude on the timing of identification	[58]
TA724	8 September 2021	Nivolumab (1L)	FP-NMA	Based on literature and subgroup analysis	–	Timing of EM/PV identification is unclear; but likely to have occurred prior to the conduct of the NMA given the focus on subgroup analysis and literature reviews	[59]
TA760	12 January 2022	Selpercatinib (2L+)	NMA	–	Based on literature and clinical advice	Timing of EM/PV identification is unclear; but likely to have occurred prior to the conduct of the NMA given the focus on expert elicitation exercises and literature reviews	[60]
TA770	9 February 2022	Pembrolizumab (1L)	Bucher ITC	Based on sensitivity analyses and clinical advice	–	EM/PV likely identified during or after the conduct of the Bucher ITC given the focus on sensitivity analyses	[61]
TA781	30 March 2022	Sotorasib (2L+)	MAIC; PSWA	Based on literature review and clinical advice	–	Timing of EM/PV identification is unclear; but likely to have occurred prior to the conduct of the MAIC given the focus on literature reviews	[62]
TA789	18 May 2022	Tepotinib (1L+)	MAIC	–	• Based on literature (unclear how results were used) • Based on clinical advice	Timing of EM/PV identification is unclear; but likely to have occurred prior to the conduct of the MAIC given the focus on literature reviews and expert elicitation exercises	[63]
TA812	3 August 2022	Pralsetinib (1L+)	PSWA	–	No information on selection process provided	Insufficient information provided to conclude on the timing of identification	[64]
TA850	14 December 2022	Amivantamab (2L+)	IPTW	Based on literature review and clinical advice	–	EM/PV identification prior to the conduct of the MAIC	[39]
TA855	4 January 2023	Mobocertinib (2L+)	IPTW	Based on literature review and clinical advice	Based on literature review and clinical advice	Timing of EM/PV identification is unclear; but likely to have occurred prior to the conduct of the IPTW given the focus on literature reviews and expert elicitation exercises	[65]

1L: First line; 2L+: Second line or later; CADTH: Canadian Agency for Drugs and Technologies in Health; EM: Effect modifier; ERG: Evidence review group; FP: Fractional polynomial; ID: Identification; IPD: Individual patient data; ITC: Indirect treatment comparison; LoT: Line of treatment; MAIC: Matching-adjusted indirect comparison; NICE: National Institute for Health and Care Excellence; NMA: Network meta-analysis; NSCLC: Non-small cell lung cancer; pERC: Pan-Canadian Oncology Drug Review Expert Review Committee; PSWA: Propensity score weighting analysis; PV: Prognostic variable; TA: Technology appraisal.

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Table 2. Health Technology Assessment Review – Non-small Cell Lung Cancer (cont.).

Submission ID	Date of Guidance	Intervention (LoT)	Type of ITC	EM Identification	PV Identification	Timing of EM/PV Identification	Ref.
CADTH							
PC0106-000	2 November 2017	Dabrafenib + trametinib (2L+)	NMA; MAIC	• Pivotal trial in NSCLC BRAF V600 mutation, with that specific mutation a-priori considered an EM by pERC • pERC noted that not all EMs had been considered	–	Timing of EM/PV identification is unclear; but likely to have occurred prior to the conduct of the NMA and MAIC given the description of differences in patient characteristics across the included trials	[66]
PC0114-000	29 March 2018	Alectinib (2L+)	NMA	• No information on selection process provided • pERC noted that not all EMs had been considered	–	Timing of EM/PV identification is unclear; but likely to have occurred prior to the conduct of the NMA and MAIC given the description of differences in patient characteristics across the included trials	[67]
PC0115-000	20 June 2018	Atezolizumab (2L+)	NMA	Patient characteristics from studies included in the NMA were investigated to detect potential EMs	–	Timing of EM/PV identification is unclear; but likely to have occurred during the conduct of the NMA given the use of interaction tests to identify potential EMs	[68]
PC0129-000	31 May 2019	Dacomitinib (1L)	NMA	–	No information on selection process provided	Insufficient information provided to conclude on the timing of identification	[69]
PC0137-000	4 January 2019	Osimertinib (1L)	Bucher ITC	Based on observed differences	–	Timing of EM/PV identification is unclear; but likely to have occurred prior to the conduct of the ITC given the description of differences in patient characteristics across the included trials	[70]
PC0153-000	31 May 2019	Pembrolizumab (1L)	Bucher ITC	Patient characteristics from studies included in the NMA were investigated to detect potential EMs	–	Timing of EM/PV identification is unclear; but likely to have occurred prior to the conduct of the ITC given the description of differences in patient characteristics across the included trials	[71]
PC0155-000	3 July 2020	Atezolizumab + bevacizumab (2L+)	NMA; MAIC	Based on observed differences	–	Timing of EM/PV identification is unclear; but likely to have occurred prior to the conduct of the NMA and MAIC given the description of differences in patient characteristics across the included trials	[72]
PC0167-000	1 August 2019	Brigatinib (2L+)	NMA; MAIC	–	Logistic regression models using trial data were used to identify PVs affecting overall response rate	Timing of EM/PV identification is unclear; but likely to have occurred prior to the conduct of the NMA and MAIC given the description of differences in patient characteristics across the included trials	[73]

1L: First line; 2L+: Second line or later; CADTH: Canadian Agency for Drugs and Technologies in Health; EM: Effect modifier; ERG: Evidence review group; FP: Fractional polynomial; ID: Identification; IPD: Individual patient data; ITC: Indirect treatment comparison; LoT: Line of treatment; MAIC: Matching-adjusted indirect comparison; NICE: National Institute for Health and Care Excellence; NMA: Network meta-analysis; NSCLC: Non-small cell lung cancer; pERC: Pan-Canadian Oncology Drug Review Expert Review Committee; PSWA: Propensity score weighting analysis; PV: Prognostic variable; TA: Technology appraisal.

Table 2. Health Technology Assessment Review – Non-small Cell Lung Cancer (cont.).

Submission ID	Date of Guidance	Intervention (LoT)	Type of ITC	EM Identification	PV Identification	Timing of EM/PV Identification	Ref.
PC0176-000	3 January 2020	Pembrolizumab (1L)	NMA	Based on observed differences	–	Timing of EM/PV identification is unclear; but likely to have occurred prior to the conduct of the NMA given the description of differences in patient characteristics across the included trials	[74]
PC0183-000	30 January 2020	Lorlatinib (2L+)	MAIC	–	• Potentially based on literature review • pERC commented that not all relevant variables were included in the analysis	Timing of EM/PV identification is unclear; but likely to have occurred prior to the conduct of the MAIC given the focus on literature reviews	[75]
PC0206-000	27 January 2021	Entrectinib (1L)	MAIC	Based on literature	–	Timing of EM/PV identification is unclear; but likely to have occurred prior to the conduct of the MAIC given the focus on literature reviews	[76]
PC0218-000	4 March 2021	Nivolumab + ipilimumab (1L)	Bucher ITC	Based on subgroup analysis	–	Timing of EM/PV identification is unclear; but likely to have occurred prior to the conduct of the ITC given the focus on subgroup analysis comparisons	[77]
PC0226-000	28 May 2021	Dabrafenib + trametinib (1L)	PSWA	–	Based on observed differences	Timing of EM/PV identification is unclear; but likely to have occurred prior to the conduct of the PSWA given the description of differences in patient characteristics across the included trials	[78]
PC0230-000	21 April 2021	Brigatinib (1L)	MAIC	• Based on previous submissions • Based on interaction tests • pERC noted that not all EMs had been considered	–	Timing of EM/PV identification is unclear; but likely to have occurred prior to the conduct of the MAIC given the focus on interaction tests and use of prior submissions to inform selection	[79]
PC0249-000	17 March 2022	Lorlatinib (1L)	NMA	• Based on literature and subgroup analysis	–	Timing of EM/PV identification is unclear; but likely to have occurred prior to the conduct of the NMA given the focus literature reviews and subgroup analyses of included trials	[80]
PC0255-000	24 August 2022	Tepotinib (1L+)	MAIC; PSWA	–	–	No information on EM/PV given	[81]
PC-0261-000	28 April 2022	Selpercatinib (1L)	NMA	–	Based on real-world data	Insufficient information provided to conclude on the timing of identification	[82]
PC-0283-000	29 September 2022	Pralsetinib (1L+)	PSWA	–	• Based on clinical advice • pERC noted that not all PVs had been considered	Timing of EM/PV identification is unclear; but likely to have occurred prior to the conduct of the NMA given the focus expert elicitation exercises	[83]

1L: First line; 2L+: Second line or later; CADTH: Canadian Agency for Drugs and Technologies in Health; EM: Effect modifier; ERG: Evidence review group; FP: Fractional polynomial; ID: Identification; IPD: Individual patient data; ITC: Indirect treatment comparison; LoT: Line of treatment; MAIC: Matching-adjusted indirect comparison; NICE: National Institute for Health and Care Excellence; NMA: Network meta-analysis; NSCLC: Non-small cell lung cancer; pERC: Pan-Canadian Oncology Drug Review Expert Review Committee; PSWA: Propensity score weighting analysis; PV: Prognostic variable; TA: Technology appraisal.

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Table 3. Health Technology Assessment Review – Psoriasis.

Submission ID	Date of Guidance	Intervention (LoT)	Type of ITC	EM Identification	PV Identification	Timing of EM/PV Identification	Ref.
NICE							
TA442	26 April 2017	Ixekizumab Retreatment (unresponsive/ intolerance)	NMA	No information on selection process provided	–	Insufficient information provided to conclude on the timing of identification	[84]
TA455	12 July 2017	Adalimumab, etanercept, ustekinumab Retreatment (unresponsive/ intolerance)	NMA	Based on literature and subgroup analysis	Based on literature and subgroup analysis	Timing of EM/PV identification is unclear; but likely to have occurred prior to the conduct of the NMA given the focus on literature reviews and trial subgroup analyses	[85]
TA475	6 September 2017	Dimethyl fumarate Retreatment (unresponsive/ intolerance)	NMA	Based on subgroup analysis	–	Timing of EM/PV identification is unclear; but likely to have occurred prior to the conduct of the NMA given the focus on trial subgroup analyses	[86]
TA511	21 March 2018	Brodalumab Retreatment (unresponsive/ intolerance)	NMA	• Based on literature • ERG noted that not all EMs had been identified	–	Timing of EM/PV identification is unclear; but likely to have occurred prior to the conduct of the NMA given the focus on literature reviews	[87]
TA521	13 June 2018	Guselkumab Retreatment (unresponsive/ intolerance)	NMA	Based on subgroup analysis	–	Timing of EM/PV identification is unclear; but likely to have occurred prior to the conduct of the NMA given the focus on trial subgroup analyses	[88]
TA574	17 April 2019	Certolizumab pegol Retreatment (unresponsive/ intolerance)	NMA	–	The submission stated that studies included in the ITC were similar in terms of PVs. Manufacturer also provided (pre-planned) subgroup analysis, but it is not clear how these subgroups had been selected.	Timing of EM/PV identification is unclear; but likely to have occurred prior to the conduct of the NMA given the focus on subgroup analyses	[89]
TA575	17 April 2019	Tildrakizumab Retreatment (unresponsive/ intolerance)	NMA	–	Based on observed differences across trials and subgroup analysis	Timing of EM/PV identification is unclear; but likely to have occurred prior to the conduct of the NMA given the focus on subgroup analyses and observed differences (part of a feasibility assessment)	[90]
TA596	21 August 2019	Risankizumab Retreatment (unresponsive/ intolerance)	NMA	Information on EMs given in the appendix only (not publicly available)	–	Timing of EM/PV identification is unclear	[91]
TA723	1 September 2021	Bimekizumab Retreatment (unresponsive/ intolerance)	NMA	The manufacturer suggested that no EMs had been clearly established in this disease area	–	Timing of EM/PV identification is unclear	[40]
TA734	7 October 2021	Secukinumab Retreatment (unresponsive/ intolerance)	NMA	Based on observed differences across trials	–	Timing of EM/PV identification is unclear; but likely to have occurred prior to the conduct of the NMA given the focus on observed differences (part of a feasibility assessment)	[92]

CADTH: Canadian Agency for Drugs and Technologies in Health; EM: Effect modifier; ERG: Evidence review group; ID: Identification; ITC: Indirect treatment comparison; LoT: Line of treatment; NICE: National Institute for Health and Care Excellence; NMA: Network meta-analysis; PV: Prognostic variable; TA: Technology appraisal.

Table 3. Health Technology Assessment Review – Psoriasis (cont.).

Submission ID	Date of Guidance	Intervention (LoT)	Type of ITC	EM Identification	PV Identification	Timing of EM/PV Identification	Ref.
CADTH							
SR0530-000	21 February 2018	Guselkumab Retreatment (unresponsive/ intolerance)	NMA	• No mention of EMs in the company submission • EMs suggested by clinical experts as part of the committee discussions	–	Insufficient information provided to conclude on the timing of identification	[93]
SR0547-000	20 June 2018	Brodalumab Retreatment (unresponsive/ intolerance)	ITC	–	–	No information on EM/PV given	[41]
SR0583-000	28 May 2019	Risankizumab Retreatment (unresponsive/ intolerance)	NMA	–	–	No information on EM/PV given	[94]
SR0624-000	21 June 2021	Tildrakizumab Retreatment (unresponsive/ intolerance)	NMA	Based on subgroup analysis	–	Timing of EM/PV identification is unclear; but likely to have occurred prior to or during the conduct of the NMA given the use of subgroup analyses to identify EMs	[95]
SR0638-000	28 October 2020	Halobetasol propionate, tazarotene Retreatment (unresponsive/ intolerance)	NMA	–	–	No information on EM/PV given	[96]
SR-0698-000	30 March 2022	Bimekizumab	NMA	Based on literature and clinical advice	–	Timing of EM/PV identification is unclear; but likely to have occurred prior to the conduct of the NMA given the focus on literature reviews and expert elicitation exercises	[97]

CADTH: Canadian Agency for Drugs and Technologies in Health; EM: Effect modifier; ERG: Evidence review group; ID: Identification; ITC: Indirect treatment comparison; LoT: Line of treatment; NICE: National Institute for Health and Care Excellence; NMA: Network meta-analysis; PV: Prognostic variable; TA: Technology appraisal.

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stated that relevant EMs (interfering factors) had been identified prior to the conduct of the ITC. Based on the limited information provided in the other submissions, it was assumed that factors had been selected either prior to or when conducting the ITC. Although literature sources were commonly cited as sources for the selection of EMs and PVs, lack of information around the sources and the identification of such evidence makes a systematic approach highly unlikely to have been conducted. Prior knowledge about the natural history of disease and research on EMs and PVs have been stated as reasons for the limited information regarding the EM selection included in the ITCs [40,41].

Across the submissions, the assessment groups generally criticised that not all interfering variables had been accounted for in the ITCs, which ultimately resulted in considerable limitations in the analysis and confidence in the ITC results. For example, in many NICE submissions, the ERG criticised that manufacturers had either not fully addressed all known factors (clinical input sought from the ERG highlighted additional EMs and PVs to consider for adjustment), not designed their efforts to identify interfering variables in a way that could establish whether such a variable is indeed an EM or PV, or not provided sufficient detail and justification for a subset of potential interfering variables being chosen for adjustment among a longer list of potential factors being considered. On the contrary, in many CADTH submissions for psoriasis, the ERG attributed the lack of EM/PV consideration to data not being available for all factors across studies. As such, addressing these limitations might not have been possible even if additional efforts to identify EMs and PVs (e.g., through additional literature review sources or expert opinion) had been undertaken.

Discussion

Comparative treatment effects for novel health technologies commonly rely on the use of indirect comparisons in the absence of head-to-head trials, based on the assumption that the distribution of EMs is similar across the study populations. While imbalance in this EM distribution can considerably bias the validity of analysis results, issues can also arise if PVs are considered interchangeable with EMs, also introducing uncertainty in the decision-making [2,7]. Yet, no clear guidance exists from HTA bodies on the "appropriate" method for identification and selection of EMs.

The current series of pragmatic reviews showed that published guidance, across different organisations and settings, on this topic was generally scarce. This is surprising given the importance of EMs in ITC methods and analysis.

The most explicit guidance was from NICE which recommended a review of the literature or structured discussions with clinical experts to inform this selection [16]. However, the guidance falls short of providing clarity on how literature reviews should be designed; for example, which type of evidence should be considered, which criteria should be applied to define the transferability of findings on EMs and PVs from other sources to the current trial and trial population, and whether a hierarchical approach to the final selection of EMs and PVs to be considered and adjusted for should be applied. Documents from HAS, PBAC and the G-BA referred to qualitative and quantitative methods to test for EMs without providing further details on the exact methods to be employed (the 2009 HAS guidance was the most recent English version that could be identified) [17–19]. Non-payer organisations mainly provided checklists for reporting ITC methods and results. Although many included specific reporting items for the EM selection process, it was not the remit of these checklists to provide clear guidance on how the selection should be conducted in practice.

In line with the lack of clear guidance by payers and non-payer organisations, this trend also continued in practice (published literature). Authors rarely provided justification for the selection of EMs in the published NMAs/ITCs. Some publications listed a-priori selected factors but did not provide additional details on how these lists had been compiled. Six published ITCs noted that the selection of EMs was based on results from a literature review whereas five articles mentioned that experts had been consulted. However, none of these reported whether a systematic approach had been applied for the identification of these factors. It is also unclear to what extent word limits by scientific journals may have contributed to the omission of such information. Despite the short timeframe of the review of published NMAs and ITCs, an early trend suggested increasing awareness of the need to provide more information on the EM selection process, with an increasing number of relevant articles identified year-on-year.

The findings from these reviews were supported by the results of reviewing previous NICE and CADTH submissions for NSCLC and psoriasis—two indications with a rapidly changing treatment landscape. In many instances, EMs appeared to have been defined a-priori (based on prior submissions on the same disease) or the selection was informed by subgroup analyses of clinical trials considered for the analysis. Clinical experts were

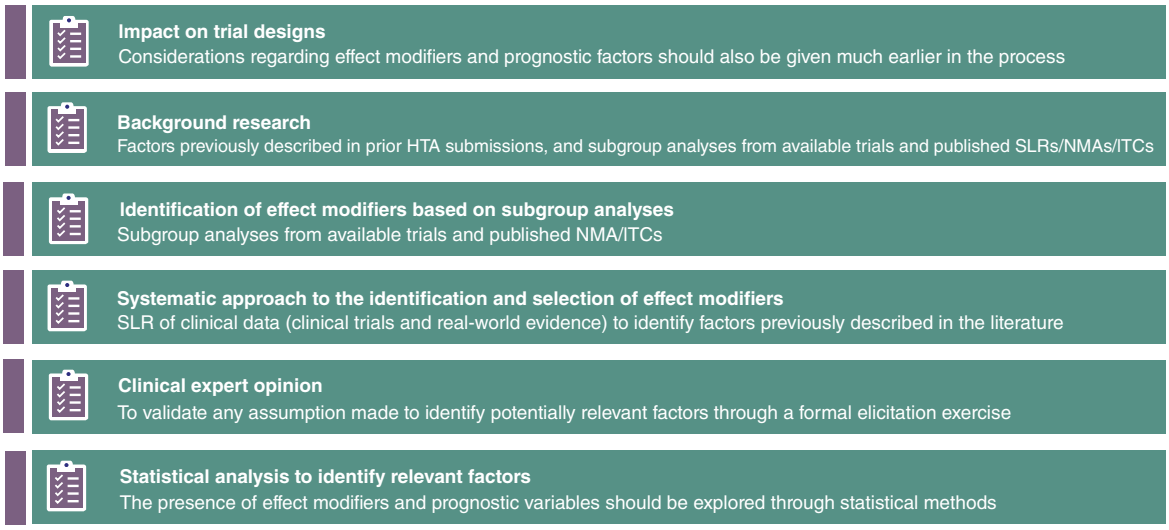

Figure 5. Recommended approaches for ensuring an unbiased identification and selection of effect modifiers.
HTA: Health technology assessment; ITC: Indirect treatment comparison; NMA: Network meta-analysis; SLR: Systematic literature review.

often involved in validating these assumptions in many submissions, in line with general requirements from HTA bodies, although this was more often explicitly stated in NICE than in CADTH submissions. Clear descriptions of a systematic identification of EMs, an important aspect in providing confidence in the ITC results, were lacking across the identified submissions.

Against this background, further research is needed to address key aspects for building an evidence base with an eye toward supporting regulatory as well as reimbursement submissions (Figure 5). SLRs may need to be tailored accordingly so that a systematic approach to the identification and selection of EMs can be applied. For example, a broad scope SLR of clinical data (both from clinical trials and real-world evidence) can be conducted to identify (1) factors previously described in the literature and prior HTA submissions, and (2) subgroup analyses from both the index trial, previously conducted trials, and published NMAs/ITCs.

A key component in HTA submissions is the integration of expert opinion to describe uncertainties associated with the clinical and cost-effectiveness of competing interventions; structured elicitation exercises have a critical role in validating some of the assumptions in the use of PVs during ITC feasibility studies but a clear documentation of the processes and its results is needed to ensure unbiased conclusions [42–44]. Another component of paramount importance to the study design is the inclusion of clinical experts to validate assumptions made during the feasibility assessment or to identify potentially relevant factors through a formal elicitation exercise. The distinction between EMs and PVs can be challenging when based solely on clinical practice experience, underscoring the need for providing experts with detailed methodological a-priori training to separate the meaning between the two definitions.

The key strength of this research is the combination and comprehensiveness of review activities (guidance frameworks, HTA submissions based on these frameworks, and published ITCs in a real-world setting) to answer the research question. Despite the relatively short timeframe for the reviews of HTA submissions and published ITCs, it is unlikely that more comprehensive information on the EM selection process is available from older publications given the clear recommendation by the NICE DSU published only in 2016 [2].

This research was limited by several factors. First, the literature searches for published ITCs were restricted by terms for EMs and PVs for practical reasons. However, this was deemed unlikely to have biased the trend around the underreporting. Given the importance of addressing interfering variables in ITCs, abstracts were considered to commonly include whether an extensive exercise to identify these factors had been conducted. Second, a pragmatic decision was made to restrict the review of HTA submissions to two representative indications both of which are associated with a rapidly evolving treatment landscape: one chronic disease and one oncology indication. EMs are relatively well established for NSCLC; however, this is not true for psoriasis. This may partially explain the lack of information on interfering factors in many of the HTA submissions for psoriasis. It should be noted that in cases

where data are not sufficiently available on interfering variables, additional (systematic) efforts to identify EMs and PVs are unlikely to result in a more comprehensive list of factors to be considered. Third, commercially sensitive information in HTA submissions is often redacted from published documents. In many CADTH submissions, the ITC relevant sections were heavily redacted, providing limited information on the analysis and any EMs and PVs considered relevant for. Some CADTH submissions had to be excluded from the review because even the analysis type was considered commercially sensitive. Finally, the lack of clear information in NICE appraisals on how interfering variables were identified may partially be due to the structure of the NICE submission template. Most NMA/ITC details are included in the appendices which are not immediately publicly available.

Conclusion

Given the evidence-based commitment by HTA bodies for using high-quality, fit-for-purpose evidence, there is a gap in guidance on how to appropriately identify EMs for inclusion in ITCs supporting HTA submissions. Adjusting for the "right" factors should be considered equally as important as choosing the appropriate ITC method. This guidance gap continues as a trend of underreporting of the identification and selection of EMs and PVs in published ITCs and company submissions for reimbursement. More explicit guidance is therefore needed on the wide range of evidence and sources needed to comprehensively identify EMs, including how to conduct SLRs on EMs and validation through formal expert elicitation. Similarly, a transparent reporting of the EM and PV selection process is required when conducting NMAs and ITCs to allow for an independent review and critique of the set of variables included for adjustment.

Executive summary

- Indirect treatment comparisons (ITC) are frequently used in health technology assessments (HTA) to evaluate the value of new treatment in absence of sufficient head-to-head evidence.
- The validity of ITCs can be impacted by differences in effect modifiers (EM) or prognostic variables (PV) across the included trials.
- ITC methodological discussions have so far been centred around the statistical properties of these methods including the assumptions around EMs and their validity, yet very little attention has been paid to how EMs are identified in the first place.
- This series of pragmatic reviews aimed to describe requirements for the appropriate selection of EMs (based on guidance documents from HTA and non-payer organisations) and how these are applied in practice (based on published ITCs and prior HTA submissions in non-small cell lung cancer and psoriasis).
- Lack of detailed guidance on how to systematically identify EMs for ITCs in the context of HTA decision-making.
- Only 17 of 511 (3.3%) reviewed ITCs included a description of the selection process for EMs and PVs; literature reviews and expert opinion were the most commonly cited sources.
- A similar trend was found across prior HTA submissions; many EMs were defined a-priori based on information from prior submissions and trial subgroup analyses and validated by clinical input.
- Providing clear guidance on the identification and selection of EMs must be considered a key research area by HTA bodies.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: https://bpl-prod.literatumonline.com/doi/10.57264/cer-2023-0046

Author contributions

A Freitag, L Gurskyte and G Sarri were responsible for study conception and design; all authors contributed equally to the literature review, and drafting and revision of the manuscript.

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