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A Targeted Review of Worldwide Indirect Treatment Comparison Guidelines and Best Practices

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ABSTRACT

Objectives: Controls and governance over the methodology and reporting of indirect treatment comparisons (ITCs) have been introduced to minimize bias and ensure scientific credibility and transparency in healthcare decision making. The objective of this study was to highlight ITC techniques that are key to conducting objective and analytically sound analyses and to ascertain circumstantial suitability of ITCs as a source of comparative evidence for healthcare interventions.

Methods: Ovid MEDLINE was searched from January 2010 through August 2023 to identify publicly available ITC-related documents (ie, guidelines and best practices) in the English language. This was supplemented with hand searches of websites of various international organizations, regulatory agencies, and reimbursement agencies of Europe, North America, and Asia-Pacific. The jurisdiction-specific ITC methodology and reporting recommendations were reviewed.

Results: Sixty-eight guidelines from 10 authorities worldwide were included for synthesis. Many of the included guidelines were updated within the last 5 years and commonly cited the absence of direct comparative studies as primary justification for using ITCs. Most jurisdictions favored population-adjusted or anchored ITC techniques opposed to naive comparisons. Recommendations on the reporting and presentation of these ITCs varied across authorities; however, there was some overlap among the key elements.

Conclusions: Given the challenges of conducting head-to-head randomized controlled trials, comparative data from ITCs offer valuable insights into clinical-effectiveness. As such, multiple ITC guidelines have emerged worldwide. According to the most recent versions of the guidelines, the suitability and subsequent acceptability of the ITC technique used depends on the data sources, available evidence, and magnitude of benefit/uncertainty.

Keywords: guidelines, health technology assessment, indirect treatment comparison, policy.

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Highlights

- Indirect treatment comparisons (ITCs) provide valuable insights into clinical-effectiveness considering the challenges of conducting head-to-head randomized controlled trials and the dynamic treatment landscape. Therefore, numerous ITC guidelines have been published by various authorities worldwide. Sixty-eight guidelines from 10 authorities worldwide were included for assessment. ITC methodology has continued to evolve, and many guidelines now include more complex ITC techniques.
- ITCs are often justified by the lack of direct comparative evidence. Most jurisdictions favored population-adjusted or anchored ITC techniques, such as network meta-analyses and population-adjusted indirect comparisons. In general, naive comparisons are not preferred because the outcomes are difficult to interpret and are prone to bias because of confounding. However, the ITC technique suitability is circumstantial and depends on the data sources, available evidence, and magnitude of benefit/uncertainty.
- This review identifies and compares the jurisdiction-specific methodology and reporting recommendations, which are key to conducting objective analyses, minimizing bias, and ensuring scientific credibility and transparency. It also highlights the global acceptance of various ITC techniques as a source of comparative evidence.

Introduction

Randomized controlled trials (RCTs) are the gold standard for studying causal relationships.[1] However, the conduct of head-to-head RCTs faces several challenges. Ethical considerations, especially in oncology and rare diseases, prevent researchers from comparing patients directly with inferior treatments or placebo.[2,3] Furthermore, the relevance of comparators in clinical trials depends on both temporal and geographical factors as the choice of comparator may vary substantially across different jurisdictions given the fast-evolving oncological treatment landscape.[4] In light of these challenges, comparative data derived from indirect treatment comparisons (ITCs) can serve as a valuable resource to provide insights on clinical-effectiveness that reflect current and local clinical practice.

Evidence from ITCs can aid regulators and reimbursement agencies in making better informed decisions to facilitate patient access to novel treatments.[5-7] The first guidelines on ITCs were published in the 1990s, with the first Cochrane guide on using individual patient data (IPD) in meta-analyses published by Stewart et al[8] in 1995 and the pivotal article on the Bucher method published in 1997 by Bucher et al.[6] Since then, various ITC techniques have been introduced that allow for the adjustment of prognostic factors and effect modifiers to address heterogeneity, evaluate consistency, and measure publication bias.

Given the substantial methodological developments in ITCs in recent years, global, regional, and national organizations have

released guidelines for such assessments, describing the best practices to minimize bias and ensure transparency in reporting. This study aimed to gather and delineate a comprehensive set of ITC requirements by consolidating information from pivotal guideline documents publicly available worldwide. Additionally, we aimed to highlight ITC techniques that are key to conducting objective and analytically sound ITC analyses and to further ascertain circumstantial suitability of ITCs as a source of comparative evidence. This review identifies the inconsistencies, gaps, and ambiguities of current ITC guidelines, thereby highlighting ways in which future guidelines can be clarified and made more comprehensive to improve transparency, reproducibility, and objectivity of ITC methods and corresponding outcomes for pricing, reimbursement, and health technology assessment (HTA) purposes.

Methods

Literature Review

A targeted literature review was conducted to identify publicly available guidelines, standards, and recommendations that mention ITC reporting and methodology. Ovid MEDLINE was searched in August 2023 by a medical information specialist. Retrieval was limited to documents published since 2010 in the English language. Hand searches of the websites of 12 prespecified international, regulatory, and HTA authorities were also performed to identify additional relevant documents published from inception to August 2023. Additional details regarding the search strategy are provided in Appendix A in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.05.015.

Document Selection and Data Extraction

Only the most recent versions of documents that met the eligibility criteria were retained if more than 1 version was identified. Documents that did not mention ITCs in any capacity or were published in a language other than English were excluded. The documents were reviewed in duplicate at each stage, and discrepancies were resolved by consensus or adjudication by a third reviewer. Various ITC techniques, including but not limited to the Bucher indirect comparison,[6] network meta-analysis (NMA),[9-11] multilevel network meta-regression (ML-NMR),[12] matching-adjusted indirect comparison (MAIC)/simulated treatment comparison (STC), and propensity score (PS) methods,[13] were searched. The documents were categorized into 3 groups based on the level of information provided:

- High-level guidelines: only mentioned ITCs in general; without providing recommendations on the reporting and presentation of specific ITC techniques.
- Detailed guidelines: providing recommendations on the reporting and presentation of specific ITC techniques.
- Comprehensive guidelines: similar to detailed guidelines but with additional guidance on the methodological conduct (ie, technical elements and statistical code).

Details regarding the data extraction are described in Appendix B in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.05.015.

Results

Literature Review

In total, 68 documents from 10 authorities worldwide were included (Fig. 1). A full list of included documents by each authority is provided in Appendix B in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.05.015. A list of the documents that were excluded after full-text assessment with rationale is provided in Appendix C in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.05.015.

The Prevalence of ITCs Guidelines Worldwide

Documents were retrieved from all 3 international organizations (n = 19), 2 of the 4 regulatory agencies (n = 10), and all 5 HTA agencies (n = 39) (Appendix B in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.05.015).

The document publication dates spanned from 2000 to 2023. However, 54 documents (79%) were published within the last 10 years, with 27 (40%) published within the last 5 years. The publication date distribution of the included documents by document type across authorities is presented in Figure 2.

International organizations

All international organizations published guidelines on ITCs, corresponding to 19 included documents. Of these, 12 guidelines were from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force, 3 were from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), and 4 were from the International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

Of the 12 guidelines from the ISPOR Task Force, 6 provided high-level guidance on ITC and were published as early as 2003.[14-19] The other 6 guidelines were detailed/comprehensive in nature and provided recommendations on the reporting and presentation of NMAs and PS methods as early as 2009.[20-25]

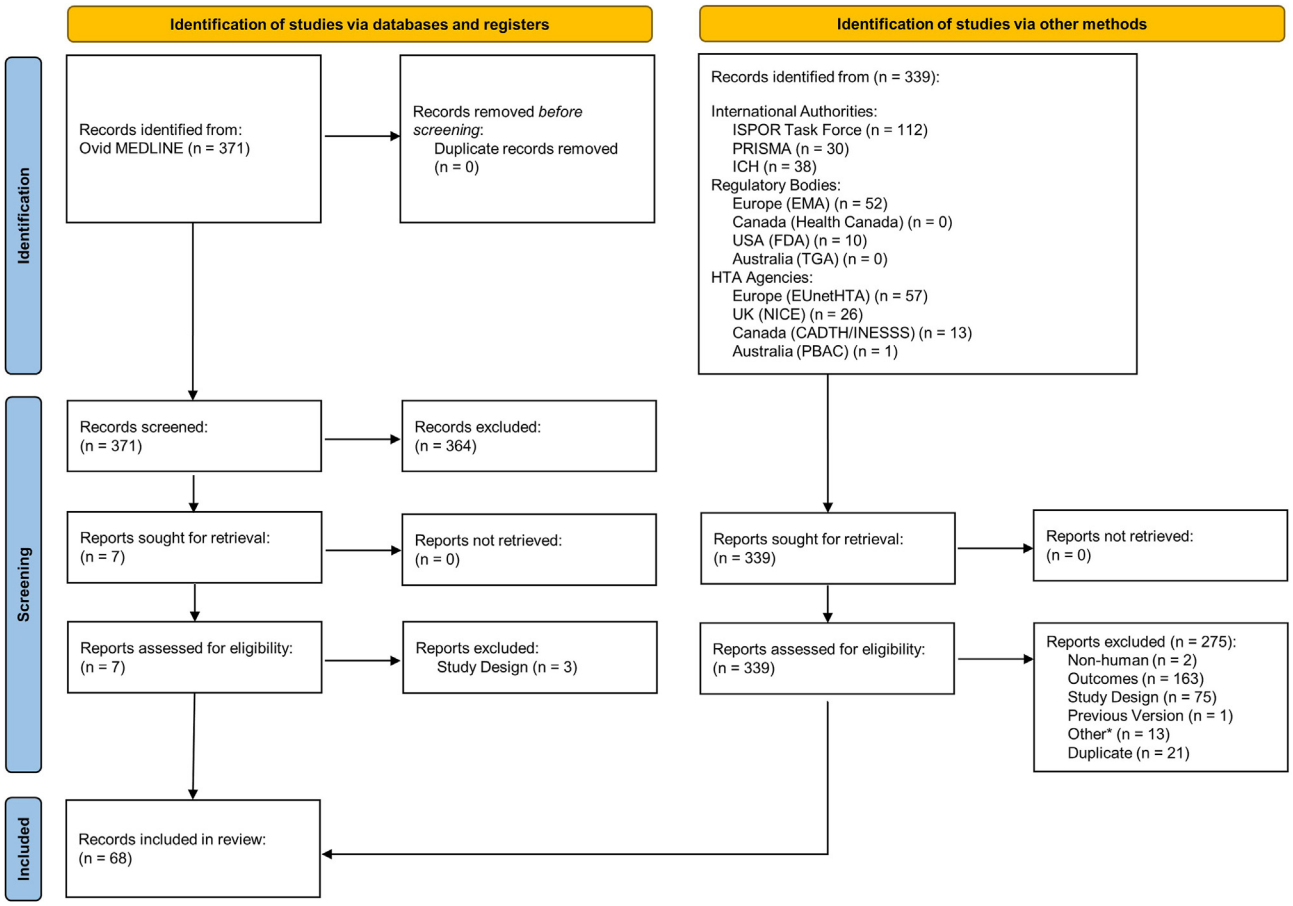
The 3 included guidelines from PRISMA were detailed and were released in 2015 and 2020. The reporting and presentation of NMAs was thoroughly discussed in the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating NMAs (PRISMA-NMA).[26] Other detailed guidelines from PRISMA also mentioned the use of the Bucher method to judge local consistency for contrasts of interventions that are part of a closed loop.[26]

Of the 4 included documents from the ICH, 2 were high level and focused primarily on clinical trials and general statistical analysis elements; however, many of the considerations discussed also apply to the assessment of indirect safety or efficacy comparisons of 2 treatments.[27,28] The first of these guidelines was published in 2000.[28] Methods for naive comparisons and NMA were briefly mentioned in another high-level document published in 2019.[29] Lastly, the most recent ICH guideline published in 2022 was detailed and provided recommendations on the reporting and presentation of NMAs. Meta-analytic techniques, specifically Bayesian and frequentist approaches to NMA, were described as methods to incorporate information from the reference population in the analysis of the target population.[30]

Regulatory agencies

Of the regulatory agencies that published guidelines, 4 were from the European Medicines Agency (EMA),[31-34] and 6 were from

Figure 1. PRISMA flow diagram. *Others include documents that are in progress at the time of this review, as well as directory pages for related documents.



CADTH indicates Canadian Agency for Drugs and Technologies in Health; EMA, European Medicines Agency; EUnetHTA, European network for Health Technology Assessment; EMA, European Medicines Agency; FDA, Food and Drug Administration; HTA, health technology assessment; ICH, International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use; INESSS, Institut national d'excellence en santé et en services sociaux; ISPOR, Society for Pharmacoeconomics and Outcomes Research; NICE, The National Institute for Health and Care Excellence; PBAC, Pharmaceutical Benefits Advisory Committee; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; TGA, Therapeutic Goods Administration; UK, United Kingdom; USA, United States of America

the US Food and Drug Administration (FDA).[35-40] All guidelines were high level. No documents were retrieved from Health Canada or the Australian Therapeutic Goods Administration.

HTA agencies

All HTA agencies published guidelines on ITCs, resulting in a total of 39 included documents. Of these, 23 were from Europe, 9 were from Canada, and 1 was from Australia.

Although 18 guidelines referencing ITCs have been released by the European Network for HTA (EUnetHTA) over the last 10 years,[41-58] only 4 were detailed/comprehensive.[42,49,52,53] As of the latest documents released in 2022, these guidelines included the Bucher, NMA, and population-adjusted indirect comparison (PAIC) techniques.[52,53] Additionally, 11 guidelines from the National Institute for Health and Care Excellence (NICE) in the United Kingdom were included; all were detailed/comprehensive.[59-63] The latest versions of these guidelines were published in 2022 and thoroughly described the reporting and methodological conduct of the aforementioned techniques, as well as ML-NMR.[59,63]

Among the included documents from Canadian HTA agencies, 8 were from the Canadian Agency for Drugs and Technologies in Health (CADTH), and 1 was from the Institut national d'excellence en santé et services sociaux (INESSS) in Quebec. Four of the included CADTH guidelines were high level and the other 4 were detailed. The earliest of the detailed guidelines was published in 2009 and illustrated the application of the Bucher method and NMA. Subsequent detailed guidelines also discussed the ML-NMR and PS methods.[64,65] The 1 included guideline from INESSS, published in 2022, was high level.[66]

Only 1 detailed guideline was included from the Australian Pharmaceutical Benefits Advisory Committee (PBAC), in which reporting considerations for the Bucher, NMA, and PAIC techniques were provided.[67]

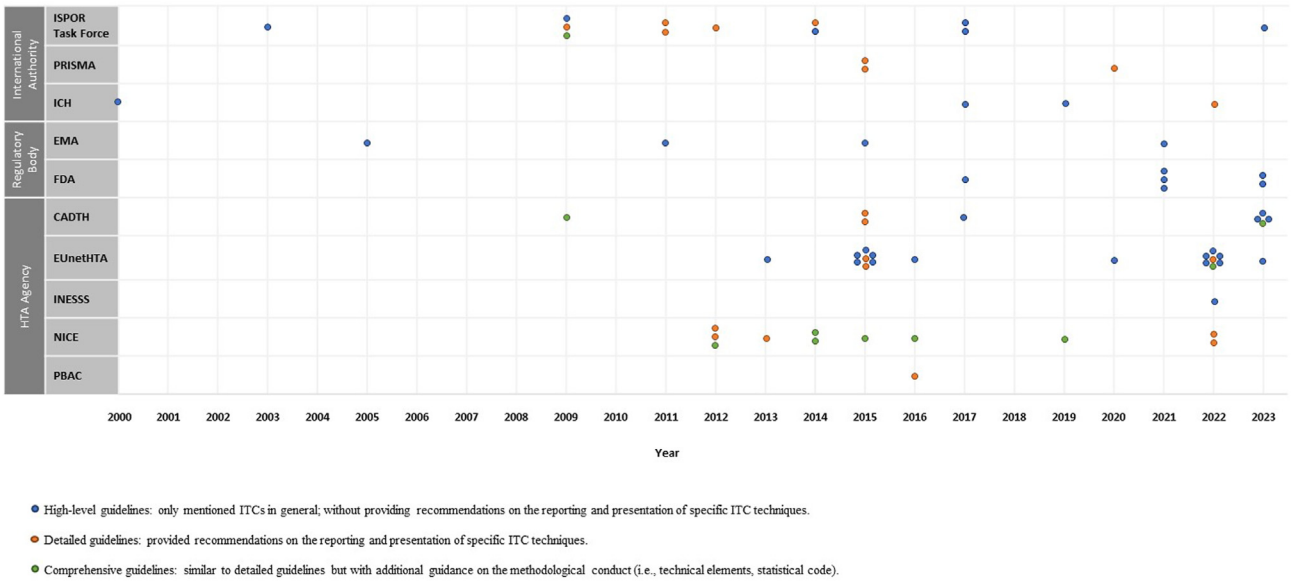
Rationale for the Application of ITCs

International organizations, regulatory agencies, and HTA agencies commonly cited the absence of direct comparative studies as a primary justification for using ITC.

International organizations

Two of the 3 included international organizations highlighted the need and benefit of ITCs in their published guidelines. Specifically, both the ISPOR ITC Good Research Practices Task Force[23] and the PRISMA-NMA[26] provided guidance on conducting research in the context of ITCs, particularly when RCTs with direct

Figure 2. Distribution of the included documents by type across authorities. Note. each dot represents an included document.



CADTH indicates Canadian Agency for Drugs and Technologies in Health; EMA, European Medicines Agency; EUnetHTA, European network for Health Technology Assessment; EMA, European Medicines Agency; FDA, Food and Drug Administration; HTA, health technology assessment; ICH, International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use; INESSS, Institut national d'excellence en santé et en services sociaux; ISPOR, Society for Pharmacoeconomics and Outcomes Research; ITC, indirect treatment comparison; NICE, The National Institute for Health and Care Excellence; PBAC, Pharmaceutical Benefits Advisory Committee; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

comparisons of all relevant treatments are missing. The ISPOR Task Force also indicated that including both direct and indirect comparisons can contribute to the total body of evidence, potentially strengthening the assessment between the evaluated treatments.[21]

Regulatory agencies

The included documents from the FDA and EMA did not provide a specific justification for the need to conduct ITCs. However, the FDA guidelines indicated that when analyzing data from externally controlled trials, several factors should be considered in the methodology to account for differences in baseline factors and confounding variables between arms across different trials.[39]

HTA agencies

In Europe, direct comparisons of medical interventions within RCTs are generally preferred for providing the best evidence of relative effectiveness. Nevertheless, EUnetHTA and NICE recognized that ITCs can serve to validate the reliability of direct evidence and allow for consideration of a larger evidence base. ITCs prove particularly discerning when faced with restricted head-to-head evidence or the simultaneous evaluation of >2 treatments.[42]

CADTH and INESSS also highlight that in many cases, direct comparisons among all comparators are limited and insufficient. In such situations, the use of ITCs has been advocated and is becoming more prevalent.[66,68]

The PBAC guidelines provided a framework for considering indirect comparisons when clinical and economic evaluations based on direct evidence are unavailable.[67]

Recommended ITC Technique Across Authorities

Based on the included guidelines, an overview of the accepted and preferred ITC techniques is provided in Table 1. Most jurisdictions recommend adjusted ITC techniques in preference to naive comparisons. Where possible, most jurisdictions favor NMAs, which facilitate simultaneous comparison of multiple treatment options,[23,53,69] and anchored MAICs/STCs, which use IPD and summary-level data to adjust for treatment effect modifiers to reduce bias risk from unobserved confounding in pairwise comparisons.[23,67,69] Similarly, PS methods are also favored because IPD are used to adjust for treatment effect modifiers and prognostic factors and emulate registrational trial populations. However, the suitability and subsequent acceptability of an ITC technique ultimately depends on the nature of the data sources (eg, summary-level data from published trials and IPD from clinical trials or real-world data), available evidence, and magnitude of benefit/uncertainty.

Figure 3 provides a summary of the selection process of the ITC techniques discussed. This flow chart was informed by the cross-sectional evaluation of the guidelines published by the ISPOR Task Force,[23,25] PRISMA,[26,70] ICH,[29,30] CADTH,[64,71] EUnetHTA,[42,52,53] NICE,[59,69,72] and PBAC.[67] The synthesized information emphasizes the nature of the data sources, data granularity, and the appropriateness of multiple (eg, simultaneous comparison of multiple data sets) versus pairwise (eg, single comparison between 2 data sets) comparisons, and the needs for individual-patient-level adjustment for prognostic factors and effect modifiers, to guide ITC technique selection.

International organizations

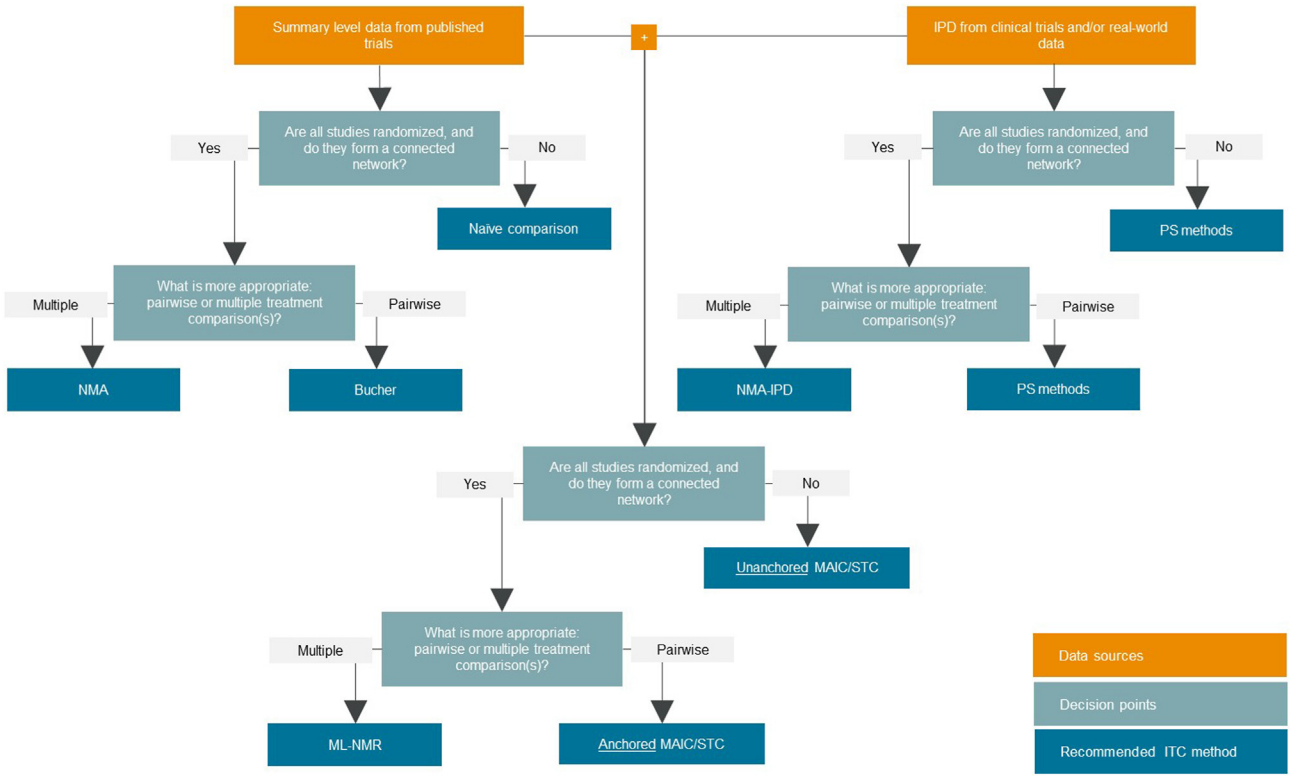
The detailed guidelines published by the ISPOR Task Force stated a preference for NMA and PS methods as formal evidence synthesis techniques and best practices that avoid potential biases that may arise when estimating intervention effectiveness and safety.[25] These guidelines also expressed that naive comparisons are prone to bias because they do not consider the difference in study effects across trials, which is deemed a fatal flaw.[21,25]

Table 1. ITC techniques among different authorities.

Expert body		Summary-level indirect comparisons			Extended summary-level Indirect Comparison	PAICs		
		Naive	Bucher	NMA	ML-NMR	MAIC/STC		PS Methods
International Organizations	ISPOR Task Force	X (2014)	–	P (2014)	–	–		P (2009)
	PRISMA	–	~ (2015)	~ (2020)	–	–		–
	ICH	X (2019)	–	~ (2022)	–	–		–
HTA Bodies	CADTH (Canada)	–	~ (2015)	~ (2023)	~ (2015)	–		~ (2023)
	EUnetHTA (Europe)	X (2022)	P (2022)	P (2022)	~ (2022)	~ Anchored (2022)	X Unanchored (2022)	~ (2022)
	NICE (UK)	X (2022)	~ (2019)	P (2022)	~ (2022)	P Anchored (2016)	~ Unanchored (2016)	~ (2022)
	PBAC (Australia)	X (2016)	P (2016)	~ (2016)	–	P Anchored (2016)	X Unanchored (2016)	~ (2016)

Note. EMA, FDA, and INESSS are not shown as their guidance regarding ITCs is very brief and does not provide information on a particular approach. The year of the most recent publication in which this information is provided is shown in parentheses.
~ indicates mentioned/discussed; –, not reported; CADTH , Canadian Agency for Drugs and Technologies in Health; FDA, Food and Drug Administration; HTA, health technology assessment; ICH, International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use; INESSS , Institut national d'excellence en santé et en services sociaux; ISPOR, Society for Pharmacoeconomics and Outcomes Research; ITC, indirect treatment comparison; EMA, European Medicines Agency; EUnetHTA, European network for Health Technology Assessment; MAIC, matching-adjusted indirect comparison; ML-NMR, multilevel network meta-regression; NICE, The National Institute for Health and Care Excellence; NMA, network meta-analysis; P, preferred; PAIC, population-adjusted indirect comparison; PBAC , Pharmaceutical Benefits Advisory Committee; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; PS, propensity score; STC, simulated treatment comparison; UK, United Kingdom; USA, United States of America; X, not accepted.

Figure 3. Selection process of ITC techniques across authorities.



IPD indicates individual patient data; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; ML-NMR, multilevel network meta-regression; NMA, network meta-analysis; PS, propensity score; STC, simulated treatment comparison. Sources: Published guidelines and best practice documents from ISPOR Task Force, PRISMA, ICH, CADTH, EUnetHTA, NICE, and PBAC.

Table 2. Recommended reporting and presentation of ITC results across authorities.

Key elements*	Bucher					NMA				
	PRISMA	CADTH	EUnet HTA	NICE	PBAC	ISPOR	PRISMA	ICH	CADTH	EUnet HTA
Evidence Base Elements										
Description of the studies considered	–	P	P	P	–	P	P	P	P	P
Description of the included populations	–	P	P	P	–	P	P	P	P	P
Assessment of heterogeneity	–	P	P	P	–	P	P	P	P	P
ITC Methods Elements										
Description of modeling framework and approach	NA	NA	NA	NA	NA	P	P	P	P	P
Description of methods for population adjustment	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Choice of priors in Bayesian NMA	NA	NA	NA	NA	NA	P	P	P	P	P
Ranking of treatments/SUCRA/P scores	NA	NA	NA	NA	NA	P	P	P	–	P
Assessment of model fit/model diagnostics	NA	NA	NA	NA	NA	P	P	P	P	P
Assessment of balance of patient baseline characteristics	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Selection of factors for adjustment	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Description of outcomes	–	P	P	P	–	P	P	–	P	P
Estimating treatment effects	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Dealing with inconsistency	NA	NA	NA	NA	NA	P	P	P	P	P
Description of sensitivity/subgroup analyses	–	P	P	P	–	P	P	P	P	P
ITC Results Elements										
Presentation of evidence base/network	NA	NA	NA	NA	NA	P	P	P	P	P
Description of study characteristics & results	–	P	P	P	–	P	P	P	P	P
Specify code/software program	–	P	–	P	–	P	P	–	P	–
Presentation of ITC results	P	P	P	P	P	P	P	P	P	P
Report of variability of aggregate measures across trials	NA	NA	NA	NA	NA	P	P	P	P	P
Demonstration of balance before/after adjustment	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Report of probability distributions	NA	NA	NA	NA	NA	P	P	P	P	P
Report of inconsistency/consistency	NA	NA	NA	NA	NA	P	P	P	P	P
Report of subgroup/sensitivity analyses	–	P	P	P	–	P	P	P	P	P
Report of convergence in Bayesian NMA	NA	NA	NA	NA	NA	–	P	–	P	P
Assessment of bias for the included RCTs	NA	NA	NA	NA	NA	P	P	–	P	P

Note. EMA, FDA, and INESSS are not shown as their guidance regarding ITCs is very brief and does not include the elements mentioned. Furthermore, the naive comparison is not shown as limited guidance was provided for ITC techniques that were deemed unfavorable/unacceptable.
– indicates not reported; CADTH, Canadian Agency for Drugs and Technologies in Health; EMA, European Medicines Agency; EUnetHTA, European network for Health Technology Assessment Joint Action; FDA, Food and Drug Administration; ICH, International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use; INESSS, Institut national d'excellence en santé et en services sociaux; ISPOR, Society for Pharmacoeconomics and Outcomes Research; ITC, indirect treatment comparison; ML-NMR, multilevel network meta-regression; NA, the key element is not applicable to the given ITC technique; NICE, The National Institute for Health and Care Excellence; NMA, network meta-analysis; P, Element recommended for inclusion in ITC; PAIC, population-adjusted indirect comparison; PBAC, Pharmaceutical Benefits Advisory Committee; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial; SUCRA, surface under the cumulative ranking curve.
*Key elements were chosen based on a review of global guidelines from various authorities and published literature. For more information, refer to region-specific guidelines and methodological conduct documents.

Table 2. Continued

NMA		ML-NMR				PAIC				
NICE	PBAC	PRISMA	CADTH	EUnetHTA	NICE	ISPOR	CADTH	EUnetHTA	NICE	PBAC
P	P	P	–	P	P	P	–	P	P	P
P	P	P	–	P	P	P	P	P	P	P
P	P	P	P	P	P	P	P	P	P	P
P	P	P	–	P	P	NA	NA	NA	NA	NA
NA	NA	–	P	P	P	P	P	P	P	P
P	P	–	–	P	P	NA	NA	NA	NA	NA
P	P	–	–	–	–	NA	NA	NA	NA	NA
P	P	–	–	P	P	–	–	–	–	–
NA	NA	–	–	P	–	–	–	P	P	–
NA	NA	–	–	P	P	–	–	P	P	P
P	P	P	P	P	P	P	–	P	P	P
NA	NA	–	–	P	P	–	–	P	P	P
P	P	P	P	P	P	NA	NA	NA	NA	NA
P	P	P	P	P	P	P	P	P	P	P
P	P	–	–	P	P	NA	NA	NA	NA	NA
P	P	P	–	P	P	P	–	P	P	P
P	P	–	–	–	P	–	–	–	P	P
P	P	P	–	P	P	P	–	P	P	P
P	P	NA	NA	NA	NA	NA	NA	NA	NA	NA
NA	NA	–	P	P	P	P	–	P	P	P
P	P	P	–	P	P	NA	NA	NA	NA	NA
P	P	–	P	P	P	NA	NA	NA	NA	NA
P	P	P	P	P	P	P	–	P	P	P
P	P	–	–	P	P	NA	NA	NA	NA	NA
P	P	P	–	P	P	NA	NA	NA	NA	NA

The PRISMA and ICH guidelines did not indicate a preferred ITC technique. However, the detailed ICH guidelines did express that a naive comparison between data sources or integration of data from multiple trials without consideration and specification of the estimand (eg, what exactly is being measured) could be misleading.[29]

Regulatory agencies

All guidelines from the EMA and FDA were high level and did not recommend a particular approach to analyzing data from externally controlled trials. However, guidelines from the EMA stated that the statistical analysis model used for estimation of treatment effects should be prespecified and include a justification for the selection and method of incorporating potential prognostic or predictive factors, as well as a discussion on how the results will be interpreted.[32] Similarly, the FDA guidelines advised that the chosen approach should effectively address and mitigate potential sources of confounding and bias. This includes developing a strategy to address discrepancies in baseline factors and confounding variables between arms across different trials.[39]

HTA agencies

In Europe, both EUnetHTA and NICE mentioned NMA as a preferred ITC technique in their detailed guidelines.[42,53,59,69] EUnetHTA also indicated a preference for the Bucher method[42,53] for straightforward star network structures while suggesting the application of NMA for more complex interconnected evidence networks.[52] In contrast, the NICE guidelines indicated an additional preference for anchored PAIC methods and only mentioned the Bucher method as an option.[9,69] Both NICE and EUnetHTA explicitly emphasized that adjusted/anchored comparisons preserve randomization and should always be used in preference to unadjusted methods or naive comparisons, where possible.[42,63]

Although the detailed CADTH guidelines emphasized good practices for conducting ITCs, they did not specify a preferred method.[64,68] The high-level INESSS guideline expressed that an ITC, published or unpublished, must be submitted when no head-to-head comparison is available. However, a particular ITC technique was not discussed.[66]

The detailed guideline from PBAC indicated that the Bucher method, as well as anchored MAICs and STCs, are preferred.[67] More specifically, it was recommended that pairwise comparisons, such as the Bucher method, are performed for each possible pathway in a network if there are multiple common comparators. Where IPD for at least 1 study in the treatment comparison are available, MAICs or STCs are preferred to correct for trial differences and to improve the transitivity of the comparison.[67]

Reporting of ITCs by Technique and Authority

Based on the accepted ITC techniques identified above, guidance was subsequently provided on the reporting of these ITCs. Although some variation in these recommendations across authorities was identified, there is overlap among the key elements (Table 2).

Notably, the recommended reporting and presentation guidelines are more consistent across authorities for the more established ITC techniques (ie, Bucher and NMA), whereas the guidance for methods that have gained traction in more recent years (ie, PAICs and ML-NMR) are more variable and less structured.

International organizations

The detailed/comprehensive ISPOR Task Force and PRISMA guidelines described how to report NMAs highlighting the importance of reporting assessment of heterogeneity and model fit, steps taken to evaluate and address inconsistency, and risk of bias for the included RCTs.[24-26] The ISPOR Task Force also requires a description of methods for population adjustment when PS methods are used (eg, PS matching/reweighting).[23] Although the Bucher method was also mentioned by PRISMA, limited guidance on the reporting and presentation of these ITCs was provided.[26]

The detailed ICH guideline discussed the reporting and presentation of NMA but not as thorough as other international organizations. When developing model-based assessments, the ICH highlighted the importance of considering the complex interrelationships (eg, correlation of parameters or assumptions).[30] Additionally, it was noted that the underlying model equations and assumptions must be clearly presented to ensure the proper assessment of their relevance to the overall strategy, model predictions, and elements of uncertainty.[30]

Regulatory agencies

Guidelines from the EMA and FDA were high level and did not include guidance on the reporting and presentation of particular ITC approaches.[31-40]

HTA agencies

From Europe, the detailed/comprehensive guidelines from EUnetHTA and NICE provided thorough recommendations on how to perform and present various ITC techniques. More specifically, the Methodological Guideline on Direct and Indirect Comparison from EUnetHTA[53] and the technical support documents published by the NICE Decision Support Unit[9,60,61,69,72-75] provide fairly consistent advice. A notable difference between these agencies was that NICE explicitly recommended that the code/software program used to conduct the ITC(s) is specified, whereas EUnetHTA did not.

The detailed guidelines from CADTH provided reporting and presentation recommendations for Bucher method and NMA that were consistent with the other authorities. However, there was more variation among the search strategy, selection of trials, methodology, assessment of heterogeneity and presentation of results for the more complex ITCs (ie, ML-NMR and PS method).[64,68,76,77]

The detailed PBAC guideline provided recommendations for NMAs that were largely consistent with those from other authorities.[67] Interestingly, although PBAC prefers simple pairwise comparisons, the reporting guidelines for this approach are not as detailed when compared with other authorities or those for more complex methods.[67]

Discussion

Considering the challenges in conducting head-to-head RCTs, ITCs can provide uniquely valuable evidence toward decision-making and reimbursement considerations. Synthesizing the information provided by global, regional, and national ITC guidelines on methodological conduct and reporting is necessary to understand the existing consistencies and discrepancies, and to identify gaps where areas of ITCs are not yet fully addressed. The objective of this study was to review the guidelines and best practices from international organizations, regulatory agencies, and HTA agencies to highlight the acceptance of ITCs as a source of comparative evidence and the reporting recommendations associated with each ITC technique. Although Health Canada and Therapeutic Goods Administration were among the regulatory agencies

searched in this review, there were no references to ITCs in their respective guidelines as they likely rely on their HTA counterparts for decision making and recommendations based on the submitted evidence. In contrast, regulatory agencies of jurisdictions where reimbursement decision making is a national responsibility (ie, the EMA and FDA) tend to view ITCs as part of addressing unmet needs, particularly when comparing against relevant comparators.

The findings from this review suggest that ITCs are accepted and recognized by authorities across Europe, North America, and Asia-Pacific, and aligned with observations that ITC methods are increasingly used.[78,79] Most guidelines explicitly mention that ITCs are particularly valuable when direct evidence is not available to provide key evidence regarding the relative benefits and harms of competing therapies. However, to reliably inform healthcare decision making, an ITC must consider the relevant comparators in each market and be tailored to the specific requirements and preferences of the given region and the respective expert body. Almost 3 decades ago, the first ITC publications and guidelines introduced the Bucher and NMA techniques. Now, authorities across the globe regularly consider evidence based upon more complex techniques that incorporate population adjustment methods (eg, MAIC/STC and PS methods). Notably, the methodology and reporting for ML-NMR has been introduced in some recent guidelines from EUnetHTA, NICE, and CADTH and proposed by Phillippo et al[12] in 2018. Furthermore, as part of the implementation of the European HTA regulation,[80] new guidance on direct and indirect comparisons have been published.[81,82]

Overall, adjusted ITC techniques are preferred over naive or unanchored comparisons in most jurisdictions. However, the appropriateness of a specific ITC technique is circumstantial, being determined by the quality of data sources, availability of evidence, and the degree of benefit or uncertainty associated with the technique. An ITC feasibility assessment may be conducted to investigate the suitability of different ITC techniques by assessing the available evidence base and the comparability and heterogeneity of the data sources, target population, and outcomes. It also identifies any barriers that may preclude such ITCs based on the available information.[9,73] Among the discussed ITC techniques, there existed a certain degree of commonality for how data sources, methods, and results should be reported across the different techniques and authorities. Although an authority may express a preference for a specific approach, this does not imply that other ITC techniques are excluded from consideration in the decision-making process. This highlights the disconnect between existing guidelines and the practical reality of what techniques and statistical methods are being used and acknowledged by the authorities, suggesting that guidelines may not be keeping pace with current practices and advancements in the field.

Although this review included a wide variety of government-appointed authorities that encompassed multiple international, regional, and national healthcare decision-making organizations, only a subset of the authorities across the globe is represented. Future efforts may broaden this scope by focusing on guidelines for specific ITC techniques, as demonstrated by Laws et al,[83] who collated national guidelines for NMAs from countries from beyond Europe and commonwealth nations. A limitation of the guideline documents themselves involved a lack of shared vocabulary, which may have affected the interpretations of the guidance provided. For instance, the terminology used for ML-NMR was inconsistent, which may be attributed to the fact that some guidelines predated the publication of the seminal article by Phillippo et al.[12] Lastly, the findings for the reporting of ITCs by technique and authority were based on a subset of the available recommendations and guidance material for select ITC techniques. Although these key elements were extracted from each guideline to provide a comprehensive overview of the most important components of reporting and presenting various ITC techniques, it is recognized that this is not an exhaustive list of criteria. Furthermore, there are other ITC techniques that are not as common because of data availability or underrepresention in the guidelines, and were therefore not discussed in this review (eg, IPD meta-analyses). Region-specific guidelines and methodological conduct documents should be consulted for more details regarding the different data sources (eg, summary level and individual level), approaches (eg, frequentist and Bayesian NMAs), and models (eg, fixed-effect and random-effects).

Our review highlights the need for authorities to develop more standardized, frequently updated, ITC guidelines to stay current with emerging techniques. Interestingly, the findings of this study are similar to recent published methodological reviews that highlight the current suboptimal practice of common ITC methods, such as PAICs. These reviews identify several hurdles, including but not limited to, covariate adjustment, the potential presence of publication and reporting bias, and heterogeneous reporting of methodological aspects, together with suggestions on how these can be overcome.[78,79] Other articles focus on methodological facets of ITC. For instance, recent criticism has been directed at STC population adjustments because of their high risk of bias, particularly in binary or time-to-event outcomes.[84] Although new methods have been proposed to address this limitation, paving the way for interesting future research in population adjustment methodology,[85] these advancements have not yet been incorporated into current guidelines. It is recognized that authorities describe the accepted ITC techniques to varying degrees; however, there is an overall lack of guidance regarding the preferred techniques to use based on the available data sources. In this absence, we generated a flow chart based on the synthesis of available guidelines. Future guidelines would be enhanced by providing specific directives that outline the preferred ITC technique for each category of data source. Furthermore, collaboration across jurisdictions may improve consistency in the conduct of ITCs through the development of more standardized ITC guidelines, facilitate the adoption of new methods, and further enhance global healthcare decision making, while also taking into consideration local needs and circumstances.

Conclusions

Recent international, regional, and national ITC guidelines recommend methods that minimize bias and ensure scientific credibility and transparency in reporting, such as NMAs using summary-level data and PAICs. Although there are some variations in the recommendations regarding the reporting and presentation of ITCs across authorities, there is overlap among the identified key elements. The suitability and subsequent acceptability of a given ITC technique is circumstantial and ultimately depends on multiple factors.

Author Disclosures

Author disclosure forms can be accessed below in the Supplemental Material section.

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